Exploring Possibilities in Nasal Polyposis Treatment at one Croatian Hospital

Mihalj, Hrvoje; Mihalj, Martina; Zubčić, Željko; Včeva, Andrijana; Laksar, Željka; Maleš, Josip

Source / Izvornik: **Medicinski Glasnik, 2012, 9, 61 - 65**

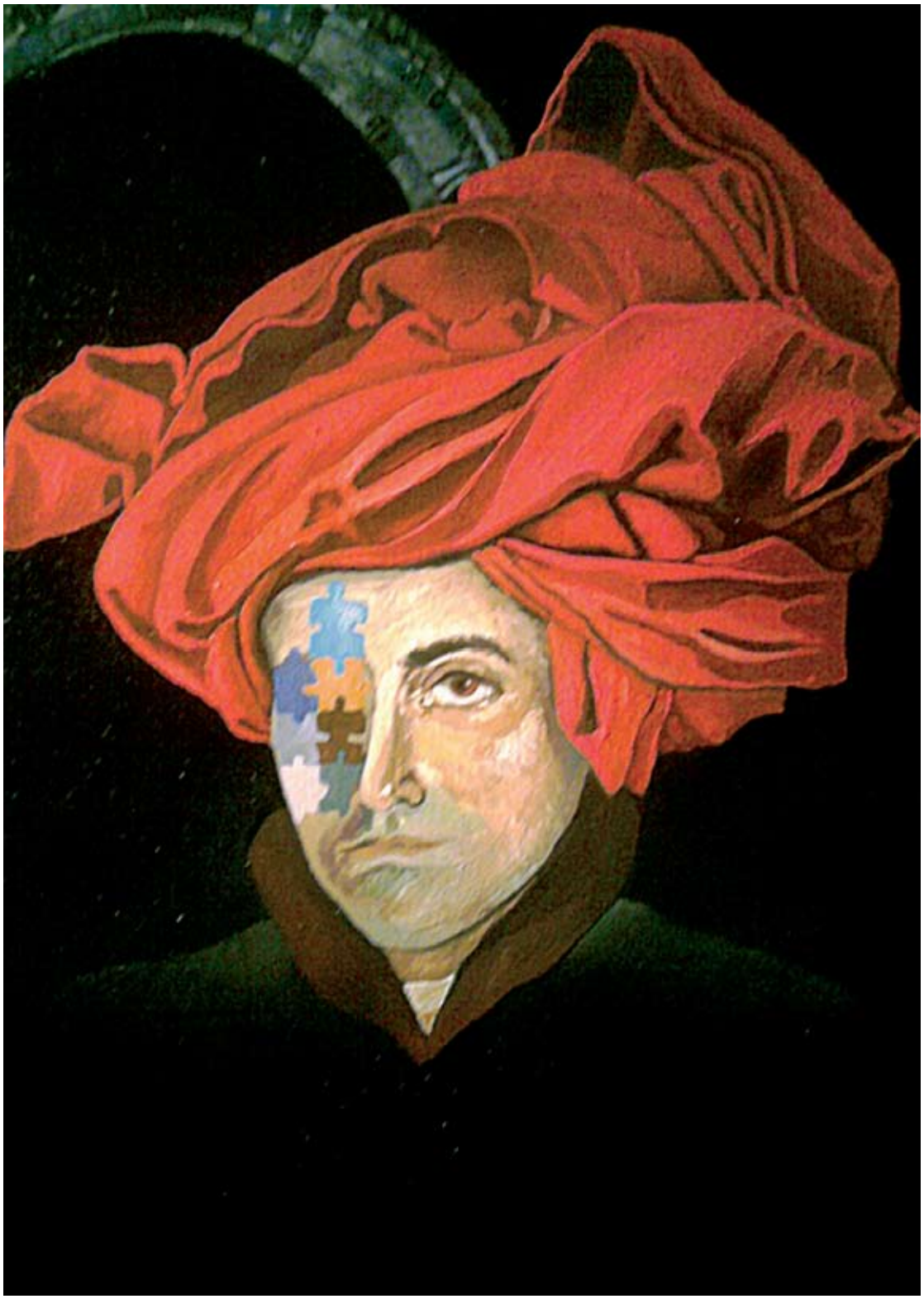
Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:239:748630

MEDICINSKI GLASNIK

Official publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina

Volume 9 Number 1, February 2012. **ISSN** 1840-0132



Tematic issue:
The hip arthroplasty – orthopedic surgery of the 20th century

Medicinski Glasnik

Official Publication of the Medical Association of
Zenica-Doboj Canton
Bosnia and Herzegovina

MEDICINSKI GLASNIK

Official Publication of the Medical Association of Zenica-Doboj Canton, Bosnia and Herzegovina
Volume 9, Number 1, February 2012
Free full-text online at: www.ljkzedo.com.ba, and www.doaj.org (DOAJ, Directory of Open Access Journals)

Content

Medicinski Glasnik is indexed by Scopus, Science Citation Index Expanded (SciSearch®), Journal Citation Reports/Science Edition, MEDLINE, EMBASE (Exerpta Medica), and EBSCO.

REVIEW

Olive oil biophenols and women's health

Ivan Fistonić[1], Mirna Šitum[2], Vedrana Bulat[2], Mario Harapin[3], Nikola Fistonić[4], Donatella Verbanac[5]

[1]Gynecology, Obstetrics and Menopause Clinic, [2]Clinic for Skin and Venereal Diseases, Clinical Hospital "Sestre milosrdnice", [3]Croatian Radio, [4]School of Medicine, University of Zagreb, [5]Centre for Translational and Clinical Research, Department of Intercellular Communication, School of Medicine, University of Zagreb; Zagreb, Croatia

ABSTRACT

Olea europea, the olive tree, is an ancient tree that originates from the Mediterranean environment of Asia Minor. The edible olive fruit is also used for its oil, gained by the process of pressing, a nutrient with proven beneficial effects. Virgin olive oil is the natural juice of the olive fruit, which plays a major role in the healthy Mediterranean diet. The source of its health effects are the biophenols and squalenes (oleocanthal, tyrosol, hydroxytyrosol, oleuropein) it contains. They provide an exceptional antioxidative activity, removing harmful compounds from the body. Oxidants are essential in the genesis of many diseases and conditions, such as cardiovascular disorders, cancer, osteoporosis, Alzheimer disease, and premenstrual syndrome. Oleic acid, an unsaturated fatty acid, has demonstrated a significant effect in the prevention of malignant diseases such as colon cancer and breast cancer. Biophenols from olive oil successfully suppress the synthesis of LDL, a protein that is crucial in the development of cardiovascular disease, by reducing blood pressure and the development of atherosclerotic plaques. In addition, there is strong evidence of the antimicrobic effect of the biphenols from olive oil that successfully destroy colonies of microorganisms which may cause respiratory tract, intestinal, and genital tract infections.

Key words: olive oil, biophenols, health

Corresponding author:
Ivan Fistonić
Gynecology, Obstetrics and Menopause Clinic
Preradovićeva 10, 10000 Zagreb, Croatia
Phone: +385 1 4855041;
fax.: +385 1 4855042;
E-mail: ivan.fistonic@zg.t-com.hr

Original submission:
29 September 2011;
Accepted:
29 October 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):1-9

INTRODUCTION

Hormonal replacement therapy (HRT) is not the only possibility to manage certian aspects of adult women's health. Huge Women's Health Initiative Study (WHI) (1) assessing the impact of HRT mainly on cardiovascular health, malignant diseases and osteoporotic fractures, have consternated not only lay users, but prescribers too. Namely, increased cancer, stroke and coronary heart disease risk associated with long term use of postmenopausal hormone therapy (HT) have rapidly declined the number of women treated with HT, either estrogen alone or estrogen plus progestogen (2). According to the recent position statements from leading organizations dealing with menopause, individualization of therapy and lower dosage HT becomes the state of the art (3). Not only WHI, but also results of other studies published in the past few years, have induced curiosity for non-estrogen containing treatments in climacteric medicine (4). Those who do not want, or interfere with hormone therapy must be given information about the merits of alternatives that are often inadequately explored. A way of life that implements a healthy Mediterranean diet allows aging with lower risk (5).

OLIVE OIL AND ITS HEALTH BENEFITS

Virgin olive oil is the result of the first and second so-called "cold" pressing of the olive fruit, without the addition of chemical substances and the use of heat. More than thirty of the structurally different olive oil biophenols that have been isolated so far originate from two fractions obtained by pressing, the glycerol (90-99%) and non-glycerol (0.4-5%) fractions (6). The biological and health benefits of olive oil are attributed to its high content of unsaturated fatty acids contained in the biophenols (7). They reduce low-density lipoprotein oxidation immediately after food ingestion (8). Additional low-density lipoprotein oxidation and peroxidation provide one of the most harmful effects on total cardiovascular health and represent a risk factor for the development of a range of chronic non-infectious diseases (9). The beneficial effect of olive oil is increased by its high percentage of mono-unsaturated oleic acid, which is less susceptible to lipid peroxidation than the poly-unsaturated fatty acids; also, its high content of alpha-tocopherol may enhance the antioxidative effect of olive oil and other vegetable oils rich in vitamin E, i.e. its fraction in the form of alpha-tocopherol (10).

Olive oil polyphenols are complex mixtures of various compounds: 3,4-dihydroxyphenyl ethanol, 4-hydroxyphenyl ethanol (tyrosol), 4-hydroxyphenylacetic acid, protocatechinic acid, syringic acid, vanillin acid, caffeic acid, and coumarin acid (11). The concentration of the phenylic fraction in olive oil varies, depending on the cultivator, climate, and ripeness of the fruit; in virgin olive oil it amounts to approximately 500 mg/L (12). Olive oil biophenols are categorized into three groups: simple phenols (tyrosol and hydroxytyrosol), secoiridoids (oleuropein and ligstroside aglycone and their decarboxylated dialdehyde derivatives), and lignans (pinoresinols) (13). They all display a high antioxidative activity; consequently, the daily intake of recommended doses of olive oil results in a considerable protective effect against colon and breast cancer, as well as skin cancer and premature aging of the skin (14, 15). From the range of components contained in olive oil polyphenols, hydroxytyrosol is the most important one. It exists as a free molecule, but is also part of complex compounds (e.g., oleuropein) (16). Laboratory tests showed that oleuropein has a stronger effect than standard antioxidats (e.g. hydroxytoluene) (17). Olive oil contains polyphenols which have a significantly greater antioxidative effect than those contained in other vegetable oils. Although most vegetable oils (sunflower, soy, rape seed) contain similar amounts of unsaturated fatty acids with attributable health benefits, they are nevertheless ineffective in fighting certain basic factors associated with chronic diseases (18). Therefore, most studies aiming to prove the benefits of olive oil use biophenols from the specific non-glycerol, non-saponifiable fraction obtained by pressing of the olive fruit (19, 20).

It is an epidemiological fact that there is a significantly lower incidence of degenerative diseases and conditions in the Mediterranean population. High-reliability studies conducted with a great number of subjects have proven that olive oil plays a key role in the beneficial effects of the so-called Mediterranean diet (21), typically characterized by a lower intake of red meat, which is substituted by white meat and plenty of fish, as well as by a daily intake of fruit, vegetables, stone fruit, and olive oil (22). Epidemiological stu-

dies recording the morbidity and mortality from potentially fatal diseases have shown that the incidence of myocardial infarction and cerebral insult, breast and colon cancer, cerebral dementia, and osteoporosis is significantly lower in the Mediterranean countries (15). This diet, part of the Mediterranean lifestyle, is undoubtedly one of the basic contributing factors of such a favorable health pattern. In addition to the diet itself, there are other typical features contributing to the mentioned health benefits: lifelong family commitments, the afternoon siesta, the controlled enjoyment of red wine, and undisturbed sleep (23).

Impact of olive oil on blood pressure

The daily intake of 50 milliliters, i.e., three table spoonfuls of olive oil has been proven to result in significant health benefits (24). A considerable number of well-designed studies showed that olive oil has a moderate, but significant lowering effect on blood pressure, due to tiny compounds contained in the olive fruit, but not found in other oils (alpha-tocopherol and specific polyphenols) (25). An experimental model showed that the pressure-lowering effect is additionally enhanced by oleic acid found in high amounts (70-80%) in olive oil (26). This acid affects the lipid component of the cell membrane (H2 passage phase) by controlling the G protein signal mediators through adenylate cyclase and C phospholipase, thus reducing blood pressure (27). By stratification, which included olive oil as a separate entity of the Mediterranean diet, a 5-year prospective EPIC study from Greece conducted with 20,343 subjects (11,658 women) without a previous history of arterial hypertension showed a considerable reduction of both systolic and diastolic pressure (-0,8 SD; (95% CI –1.1, –0.6; < 0.001) (28). A random controlled study involving hypertensive subjects on various diet regimens over the course of one year showed that extra virgin olive oil reduced the need for conventional medication, probably due to the mechanism of nitric oxide increase (29).

Olive oil reduces the risk of coronary disease by lowering cholesterol levels and an accompanying antiinflammatory effect

Almost all epidemiological and metabolic studies have found that unsaturated fatty acids reduce the risk of coronary disease. A study involving 148 women and 700 men proved that the daily use of olive oil in food preparation significantly reduces the risk of ischemic heart disease, and that as much as 47% fewer coronary incidents were recorded in the subject group which used olive oil on a daily basis, regardless of their different health profiles and lifestyles (30).

Olive oil reduces oxidation and levels of the LDL cholesterol fraction whose oxidation is partly responsible for the development of atherosclerosis (31). Simultaneously, it raises the levels of protective HDL cholesterol. Olive oil polyphenols decrease oxidative stress by removing free radicals, the malignant toxic products of oxidation (32). Biophenols contained in virgin olive oil inhibit the cell oxidation of LDL by increasing the mRNA transcription of glutathione enzymes (33).

Inflammation plays a key role in the pathogenesis of atherosclerosis. Carluccio MA et al. have discovered that olive oil reduces the concentration of cytokines (interleukin 6, TNFα, IFNγ), molecules which stimulate the inflammatory response in the vessel walls by activating monocytes and producing macrophages in the early stages of atherogenesis (34). The effect is the same as that produced by conventional antiinflammatory drugs such as ibuprofen (35).

Olive oil reduces the deposits of free fatty acids in the liver

Uncontrolled intake of fats and carbonated sweet drinks as well as increased levels of blood sugar accompanied by a rise in oxidative stress result in increased triglyceride deposits in the liver (36). An olive oil-rich diet will prevent the formation of such deposits of dangerous fats, regulate the levels of sugar and glucagon-like peptide-1 in insulin-resistant diabetics, and simultaneously enhance the action of sugar transporters (transporters 2) within the liver metabolism (37).

Olive oil biophenols reduce body weight

Studying obesity as a consequence of the urge for an excessive food intake, researchers have found that eating stimulates the cells in the intestinal epithelial mucosa to produce oleoylethanolamide (OEA), a transport medium for fats. OEA, influenced by oleic acid from olive oil, acts as a sensor for additional food intake (38). In other words, olive oil provides the feeling of satiety.

A diet rich in unsaturated fatty acids from olive oil reduces waist girth, one of the significant indicators of metabolic disease, along with a reduction in the body mass index (39).

Malignant tumors and olive oil

Olive oil contains a number of compounds which by their antioxidative action reduce the risk of cell damage and their consequential uncontrolled growth and division (40). In addition to oleic acid, such effects are provided by squalenes, tocopherol (vitamin E), and other biophenols (41).

According to experimental models, olive oil may affect all the phases of carcinogenesis. According to Adler et al., an experimental study on mice showed that resveratrol, one of olive oil biophenols, inhibits the action of NFκB transcription factor, which in turn inhibits caspases, key enzymes for cell apoptosis, and thus stops the autonomous growth of tumor cells (42, 43). Olive oil compounds such as resveratrol, hydroxytyrosol, tyrosol, oleic acid, and oleuropein induce apoptosis mediated by the Fas/Fas ligand, stimulate tumor suppressor protein p53 activity, and remove cyclin-dependent kinases 1 and 2 during the cell cycle (44).

In addition, resveratrol also inhibits angiogenesis, which is yet another way of inhibiting carcinogenesis (44).

The incidence of colon cancer has been shown to be significantly lower in those who use olive oil as part of their daily diet (45). *Helicobacter pylori* is a microorganism involved in the pathogenesis of gastric ulcer and certain types of stomach cancer. Experimental models have shown that biophenols from olive oil demonstrate a high antimicrobial activity against eight biotypes of the *H. pylori* bacterium, three of which are even resistant to antibiotic treatment (46). These results raised speculations about olive oil acting as a chemopreventive agent in the pathogenesis of gastric ulcer. However, this biological action is yet to be proven in clinical trials.

A group from the Institute of Oncology from Granada, Spain, has obtained remarkable results using an experimental *in vitro* model of MCF-7 and SKBR3 breast cancer cells. They managed to prove that that extra virgin olive oil biophenols drastically reduce the process of division and dissemination of the most malignant breast cancer types by down-regulation of the human epidermal growth factor receptor 2 (HER-2) expression and activity in cultivated breast cancer cells (47). Hydroxytyrosol, tyrosol, oleic acid, the lignans pinoresinol and 1-/+acetoxypinoresinol as well as the secoiridoids oleuropein and oleueropein aglycone, demonstrated strong tumoricidal effects through the induction of cell apoptosis in HER-2 positive cells (48). Moreover, olive oil biophenols enhance the growth inhibitory effects of *trastuzumab* (monoclonal HER-2 antibody) in breast cancer cells with Her-2/neu oncogene amplification (49). However, *in vitro* concentrations used in the study were significantly higher than those used in daily life (47).

Breast tissue density is one of the biggest risks for overlooking suspicious shadows during mammogram analysis (50). A study carried out by a group of Italian researchers showed that olive oil biophenols in the Mediterranean diet significantly decreased the density of breast tissue in mammography imaging (51).

A case-control study from Greece estimated that increasing intake of monounsaturated fat, mostly olive oil, by about one standard deviation was associated with a 26% risk reduction of endometrial cancer (OR 0.74; 95% CI 0.54-1.3) (52).

Multiple sclerosis and Alzheimer disease

A one-year double-blind random study investigated how various dietary regimens affected subjects with multiple sclerosis. In the study group on the olive oil-based diet recommended by the North American Society of Cardiology (AHA Step I diet), as compared to the conventional "Fish Oil" diet with an increased intake of omega-3 fatty acids, a significantly reduced symptomatology regarding exhaustion and tiredness was recorded already within the first 6 months (53).

Epidemiological studies showed that the Mediterranean population is notably less affected by Azheimer disease, a fact that was attributed to the above-average intake of olive oil (54, 55). A revolutionary experimental study on laboratory animals has shown that oleocanthal, the olive oil biophenol, not only enhances the signal transmission between nerve cells by blocking toxic beta-amyloid proteins in the synapses, but also aids new cell growth in the subgranular zone of the hippocampus and the subventricular zone of the lateral

ventricles (56). Those brain centers are responsible for memory and cognitive processes, mental abilities significantly impaired in patients whose cognition degenerates either by aging or due to the neurodegenerative Alzheimer disease (57).

The skin and olive oil

Olive oil contains polyphenols such as squalene, tocopherol, and resveratrol, important antioxidative agents in the prevention of a number of dermatoses (58). Resveratrol in particular has been studied recently for its influence on the slowing of skin aging.

Resveratrol stimulates the activity of sirtuin, a life-prolonging factor for fibroblasts, cells responsible for the production of collagen (59). Since collagen is the basic component of the extracellular dermal matrix whose amounts diminish during aging (60), the importance of olive oil in slowing the aging process of the skin is indisputable.

According to various studies, nicotinamide-adenine-dinucleotide (NAD), an oxidoreductase co-enzyme, inhibits the effect of sirtuin (SIRT1) (61). However, resveratrol inhibits the interaction between the NAD co-enzyme and sirtuin, thus enabling its beneficial effect on the fibroblasts (62). The amount of resveratrol necessary to stop the skin aging process has not been determined yet; besides, the marked chemical instability of this compound presents a considerable difficulty in the technological production process (63). Almost one third of the composition of olive oil is made up by a polyunsaturated fatty acid called linolenic acid, which inhibits cyclooxygenase as well as E_2 prostaglandin synthesis (64). Prostaglandin E_2 is an important inflammatory mediator present in common dermatoses such as psoriasis and atopic dermatitis (65), and the topical application of olive oil in the chronic phase of the disease decreases prostaglandin levels in the dermis, thus reducing the inflammatory response (66).

In addition to linolenic acid, the biophenol oleocanthal, isolated from virgin olive oil, has been proven to have an antiinflammatory effect due to its action as a non-selective cyclooxygenase inhibitor and cortisol receptor blocker (35).

Olive oil reduces the concentration of antiinflammatory cytokines interleukin 6, TNFα, and IFNγ, which play a key role in the immunopathogenesis of psoriasis (35).

In everyday dermatological clinical practice, olive oil is used for the prevention of irritative and allergic contact dermatitis because it is neither an irritant nor an allergen, according to the chemical compound register of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) (67). An epidemiological study carried out by the ECETOC proved that olive oil is not a sensitizer because it does not chemically react with peptides in the epidermis, which contain nucleophilic amino acids such as cystein and lysine. Topical application of olive oil creates a protective lipid film over the *stratum corneum* which prevents the absorption of irritants and allergens. The period of action of the topically applied olive oil amounts to approximately four hours (68).

Experimental models on mice have shown that topical application of olive oil inhibits the early phase of herpes simplex virus type 1 and 2 as well as varicella-zooster virus replication (69, 70).

OLIVE OIL BIOPHENOLS TARGETING SPECIFFIC ISSUES

Premenstrual syndrome (PMS) is typically characterized by irritability, difficulty concentrating, insomnia, bloating and edema, painful periods and breast tenderness, nausea, and diarrhea. By reducing oxidative processes in the brain, vitamin E, triterpenes, and phenols contained in olive oil significantly decrease PMS-related mood swings. Linoleic acid reduces the transformation of arachidonic acid into prostaglandin (PgE2) (71), a powerful hormone which affects the uterus and is thus responsible for its painful contractions during periods (72). Oleocanthal, by binding to cortisol receptors, reduces the inflammatory reaction and consequential edema, i.e., indirectly controls body weight in the second phase of the menstrual cycle (73).

Sexual lubrication of the vagina by olive oil application may have a detrimental effect on sperm motility and fertilization potential, and is thus not recommended for couples undergoing treatment for infertility (74).

An experimental model showed that bone remodeling was more pronounced in laboratory animals which had been treated with a polyphenol-rich diet (75). Only one study so far suggests a possible influence of olive oil on bone mass ma-

intenance and osteoporosis prevention; its results showed that women on a Mediterranean diet rich in olive oil had better bone density levels than those on a standard diet (76).

Research has shown that high-quality olive oil reduces low-density lipoprotein (LDL) peroxidation to a significantly higher extent than sunflower oil in hypercholesterolemic postmenopausal women (77).

Extra virgin olive oil is the best nutritional supplement for pregnant women, due to its ideally balanced nutritionally valuable fats important for intrauterine fetal development as well as the optimal fatty tissue development during early infancy (78).

In conclusion, the nutritional value of olive oil exceeds its gastronomic effect. One of the most important components of the Mediterranean diet, olive oil is not just a dietary supplement, but also an important preventive factor in the pathogenesis of numerous degenerative diseases and conditions.

ACKNOWLEDGEMENTS

The authors wish to thank molecular biologists Mihaela Perić, PhD, Hana Čipčić-Paljetak, PhD, and Mario Matijašić, MA, for their suggestions and help in the realization of this paper.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Writing Group for the Women's Health Initiative. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized control trial. JAMA 2002; 288:321-33.
2. Faber A, Bouvy ML, Loskamp L, van de Berg PB, Egberts TCG, de Jong-van den Berg LTW. Dramatic change in prescribing of hormone replacement therapy in the Netherlands after publication of the Million Women Study: a follow-up study. Br J Clin Pharmacol 2005; 60:641-7.
3. Pines A. Guidelines and recommendations on hormone therapy in the menopause. J Midlife Health. 2010; 1:41-2.
4. Albertazzi P. Non-estrogenic approaches for the treatment of climacteric symptoms. Climacteric 2007; 10:115-20.
5. Fistonić I, Canić T, Duić Z, Fistonić M, Ciglar S. Alternative hormone therapy in postmenopause. Lijec Vjesn 2006; 128:99-104.
6. Marrugat J, Covas MI, Fitó M, Schröder H, Miró-Casas E, Gimeno E, López-Sabater MC, de la Torre R, Farré M; SOLOS Investigators. Effects of differing phenolic content in dietary olive oils on lipids and LDL oxidation--a randomized controlled trial. Eur J Nutr 2004; 43:140-7.
7. Fitó M, de la Torre R, Farré-Albaladejo M, Khymenetz O, Marrugat J, Covas MI. Bioavailability and antioxidant effects of olive oil phenolic compounds in humans: a review. Ann Ist Super Sanita 2007; 43:375-81.
8. Vissers MN, P L Zock PL, Katan MB. Bioavailability and antioxidant effects of olive oil phenols in humans: a review. European Journal of Clinical Nutrition 2004; 58:955–65.
9. Perrella J, Berco M, Cecutti A, Gerulath A, Bhavnani BR. Potential role of the interaction between equine estrogens, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) in the prevention of coronary heart and neurodegenerative diseases in postmenopausal women. Lipids Health Dis 2003; 2:4.
10. Gillingham LG, Harris-Janz S, Jones PJ. Dietary monounsaturated fatty acids are protective against metabolic syndrome and cardiovascular disease risk factors. Lipids 2011; 46:209-28.
11. Konstantinidou V, Covas MI, Muñoz-Aguayo D, Khymenets O, de la Torre R, Saez G, Tormos Mdel C, Toledo E, Marti A, Ruiz-Gutiérrez V, Ruiz Mendez MV, Fito M. In vivo nutrigenomic effects of virgin olive oil polyphenols within the frame of the Mediterranean diet: a randomized controlled trial. FASEB J 2010; 24:2546-57.
12. Cicerale S, Lucas L, Keast R. Biological activities of phenolic compounds present in virgin olive oil. Int J Mol Sci 2010; 11:458–79.
13. El Riachy M, Priego-Capote F, León L, Rallo L, Luque de Castro MD. Hydrophilic antioxidants of virgin olive oil. Part 1: Hydrophilic phenols: A key factor for virgin olive oil quality. European Journal of Lipid Science and Technology 2011; 113:678–91.
14. Gibson TM, Ferrucci LM, Tangrea JA, Schatzkin A. Epidemiological and clinical studies of nutrition. Semin Oncol 2010; 37:282-96.
15. Psaltopoulou T, Kosti RI, Haidopoulos D, Dimopoulos M, Panagiotakos DB.Olive oil intake is inversely related to cancer prevalence: a systematic review and a meta-analysis of 13800 patients and 23340 controls in 19 observational studies. Lipids in Health and Disease 2011; 10:127.
16. Miro-Casas E, Covas MI, Farre M, Fito M, Ortuño J, Weinbrenner T, Roset P, de la Torre R. Hydroxytyrosol disposition in humans. Clin Chem 2003; 49:945-52.

17. Andreadou I, Iliodromitis EK, Mikros E, Constantinou M, Agalias A, Magiatis P, Skaltsounis AL, Kamber E, Tsantili-Kakoulidou A, Kremastinos DT. The olive constituent oleuropein exhibits anti-ischemic, antioxidative, and hypolipidemic effects in anesthetized rabbits. J Nutr 2006; 136:2213-9.
18. Parnham MJ, Verbanac D. Mild plant and dietary immunomodulators. In: Nijkamp FP, Parnham MJ (eds.). Principles of Immunopharmacology. 3rd revised and extended edition. Basel: Springer AG 2011: 451-72.
19. Cicerale S, Lucas L, Keast R. Biological activities of phenolic compounds present in virgin olive oil. Int J Mol Sci 2010; 11:458-79.
20. Tripoli E, Giammanco M, Tabacchi G, Di Majo D, Ciammanco S, La Guardia M. The phenolic compounds of olive oil: structure, biological activity and beneficial effects on human health. Nutr Res Rev 2005;18: 98-112.
21. Pérez-Martínez P, García-Ríos A, Delgado-Lista J, Pérez-Jiménez F, López-Miranda J. Mediterranean diet rich in olive oil and obesity, metabolic syndrome and diabetes mellitus. Curr Pharm Des 2011;17: 769-77.
22. Cicerale S, Lucas L, Keast R. Antimicrobial, antioxidant and anti-inflammatory phenolic activities in extra virgin olive oil. Curr Opin Biotechnol 2011 [Epub ahead of print]
23. Waterman E, Lockwood B. Active components and clinical applications of olive oil. Altern Med Rev 2007; 12:331-42.
24. Panagiotakos D, Pitsavos C, Chrysohoou C, Pallíou K, Lentzas I, Skoumas I, Stefanadis C. Dietary patterns and 5-year incidence of cardiovascular disease: a multivariate analysis of the ATTICA study. Nutr Metab Cardiovasc Dis 2009; 19:253-63.
25. López-Miranda J, Pérez-Jiménez F, Ros E, De Caterina R, Badimón L, Covas MI, Escrich E, Ordovás JM, Soriguer F, Abiá R, de la Lastra CA, Battino M, Corella D, Chamorro-Quirós J, Delgado-Lista J, Giugliano D, Esposito K, Estruch R, Fernandez-Real JM, Gaforio JJ, La Vecchia C, Lairon D, López-Segura F, Mata P, Menéndez JA, Muriana FJ, Osada J, Panagiotakos DB, Paniagua JA, Pérez-Martinez P, Perona J, Peinado MA, Pineda-Priego M, Poulsen HE, Quiles JL, Ramírez-Tortosa MC, Ruano J, Serra-Majem L, Solá R, Solanas M, Solfrizzi V, de la Torre-Fornell R, Trichopoulou A, Uceda M, Villalba-Montoro JM, Villar-Ortiz JR, Visioli F, Yiannakouris N. Olive oil and health: summary of the II international conference on olive oil and health consensus report, Jaén and Córdoba (Spain) 2008. Nutr Metab Cardiovasc Dis 2010; 20:284-94.
26. Bermudez B, Lopez S, Ortega A, Varela LM, Pacheco YM, Abia R, Muriana FJ. Oleic acid in olive oil: from a metabolic framework toward a clinical perspective. Curr Pharm Des 2011; 17:831-43.
27. Terés S, Barceló-Coblijn G, Benet M, Alvarez R, Bressani R, Halver JE, Escribá PV. Oleic acid content is responsible for the reduction in blood pressure induced by olive oil. Proc Natl Acad Sci U S A 2008; 105:13811-6.
28. Psaltopoulou T, Naska A, Orfanos P, Trichopoulos D, Mountokalakis T, Trichopoulou A. Olive oil, the Mediterranean diet, and arterial blood pressure: the Greek European Prospective Investigation into Cancer and Nutrition (EPIC) study. American Journal of Clinical Nutrition 2004; 80:1012-18.
29. Ferrara LA, Raimondi AS, d'Episcopo L, Guida L, Dello RA, Marotta T. Olive oil and reduced need for antihypertensive medications. Arch Intern Med 2000; 160:837-42.
30. Kontogianni MD, Panagiotakos DB, Chrysohoou C, Pitsavos C, Zampelas A, Stefanadis C. The impact of olive oil consumption pattern on the risk of acute coronary syndromes: The CARDIO2000 case-control study. Clin Cardiol 2007; 30:125-9.
31. Masella R, Varì R, D'Archivio M, Di Benedetto R, Matarrese P, Malorni W, Scazzocchio B, Giovannini C. Extra virgin olive oil biophenols inhibit cell-mediated oxidation of LDL by increasing the mRNA transcription of glutathione-related enzymes. J Nutr 2004; 134:785-91.
32. Fitó M, Cladellas M, de la Torre R, Martí J, Alcántara M, Pujadas-Bastardes M, Marrugat J, Bruguera J, López-Sabater MC, Vila J, Covas MI; members of the SOLOS Investigators. Antioxidant effect of virgin olive oil in patients with stable coronary heart disease: a randomized, crossover, controlled, clinical trial. Atherosclerosis 2005; 181:149-58.
33. Cicerale, S., Conlan, X. A., Sinclair, A. J., & Keast, R. S. J. Chemistry and health of olive oil phenolics. Critical Reviews in Food Science and Nutrition 2009;49:218-36.
34. Carluccio MA, Massaro M, Scoditti E, De Caterina R. Vasculoprotective potential of olive oil components. Mol Nutr Food Res 2007; 51:1225-34.
35. Beauchamp GK, Keast RS, Morel D, Lin J, Pika J, Han Q, Lee CH, Smith AB, Breslin PA. Phytochemistry: ibuprofen-like activity in extra-virgin olive oil. Nature 2005; 437:45-6.
36. Assy N, Nassar F, Nasser G, Grosovski M. Olive oil consumption and non-alcoholic fatty liver disease. World J Gastroenterol 2009; 15:1809-15.
37. Hansen KB, Rosenkilde MM, Knop FK, Wellner N, Diep TA, Rehfeld JF, Andersen UB, Holst JJ, Hansen HS. 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. J Clin Endocrinol Metab 2011; 96:E1409-17.
38. Schwartz GJ, Fu J, Astarita G, Li X, Gaetani S, Campolongo P, Cuomo V, Piomelli D. The lipid messenger OEA links dietary fat intake to satiety. Cell Metab 2008; 8:281-8.
39. Paniagua JA, Gallego de la Sacristana A, Romero I, Vidal-Puig A, Latre JM, Sanchez E, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Monounsaturated Fat–Rich Diet Prevents Central Body Fat Distribution and Decreases Postprandial Adiponectin Expression Induced by a Carbohydrate-Rich Diet in Insulin-Resistant Subjects. Diabetes Care 2007; 30:1717-23.
40. Ilavarasi K, Kiruthiga PV, Pandian SK, Devi KP. Hydroxytyrosol, the phenolic compound of olive oil protects human PBMC against oxidative stress and DNA damage mediated by 2,3,7,8-TCDD. Chemosphere 2011; 84:888-93.
41. Obied HK, Prenzler PD, Konczak I, Rehman AU, Robards K. Chemistry and bioactivity of olive biophenols in some antioxidant and antiproliferative in vitro bioassays. Chem Res Toxicol 2009; 22:227-34.
42. Adler AS, Kawahara TL, Segal E, Chang HY. Reversal of ageing by NFkappaB blockade. Cell Cycle 2008; 7:556-9.

43. Adler AS, Sinha S, Kawahara TL, Zhang JY, Segal E, Chang HY. Motif module map reveals enforcement of ageing by continual NfkappaB activity. Genes Dev 2007; 21:3244-57.
44. Bråkenhielm E, Cao R, Cao Y. Suppression of angiogenesis, tumor growth, and wound healing by resveratrol. The FASEB Journal 2001; 15:1798–800.
45. Hashim YZ, Eng M, Gill CI, McGlynn H, Rowland IR. Components of olive oil and chemoprevention of colorectal cancer. Nutr Rev 2005; 63:374-86.
46. Romero C, Medina E, Vargas J, Brenes M, De Castro A. In vitro activity of olive oil polyphenols against Helicobacter pylori. J Agric Food Chem 2007; 55:680-6.
47. Menendez JA, Vazquez-Martin A, Garcia-Villalba R, Carrasco-Pancorbo A, Oliveras-Ferraros C, Fernandez-Gutierrez A, Segura-Carretero A. Anti-HER2 (erbB-2) oncogene effects of phenolic compounds directly isolated from commercial Extra-Virgin Olive Oil (EVOO). BMC Cancer 2008; 8:377.
48. Menendez JA, Papadimitropoulou A, Vellon L, Lupu R. A genomic explanation connecting "Mediterranean diet", olive oil and cancer: oleic acid, the main monounsaturated fatty acid of olive oil, induces formation of inhibitory "PEA3 transcription factor-PEA3 DNA binding site" complexes at the Her-2/neu (erbB-2) oncogene promoter in breast, ovarian and stomach cancer cells. Eur J Cancer 2006; 42:2425-32.
49. Menendez JA, Vellon L, Colomer R, Lupu R. Oleic acid, the main monounsaturated fatty acid of olive oil, suppresses Her-2/neu (erbB-2) expression and synergistically enhances the growth inhibitory effects of trastuzumab (Herceptin) in breast cancer cells with Her-2/neu oncogene amplification. Ann Oncol 2005; 16:359-71.
50. Conner P. Breast response to menopausal hormone therapy-aspects on proliferation, apoptosis and mammographic density. Ann Med 2007; 39:28-41.
51. Masala G, Ambrogetti D, Assedi M, Giorgi D, Del Turco MR, Palli D. Dietary and lifestyle determinants of mammographic breast density. A longitudinal study in a Mediterranean population. International Journal of Cancer 2006; 118:1782–9.
52. Tzonou A, Lipworth L, Kalandidi A, Trichopoulou A, Gamatsi I, Hsieh CC, Notara V, Trichopoulos D. Dietary factors and the risk of endometrial cancer: a case--control study in Greece. Br J Cancer. 1996; 73:1284-90.
53. Weinstock-Guttman B, Baier M, Park Y, Feichter J, Lee-Kwen P, Gallagher E, Venkatraman J, Meksawan K, Deinehert S, Pendergast D, Awad AB, Ramanathan M, Munschauer F, Rudick R. Low fat dietary intervention with omega-3 fatty acid supplementation in multiple sclerosis patients. Prostaglandins Leukot Essent Fatty Acids 2005; 73:397-404.
54. Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Mediterranean diet and risk for Alzheimer's disease. Annals of Neurology 2006; 59:912–21.
55. Materljan E, Materljan M, Materljan B, Vlacić H, Barićev-Novaković Z, Sepcić J. Multiple sclerosis and cancers in Croatia - a possible protective role of the "Mediterranean diet". Coll Antropol 2009; 33:539-45.
56. Valente T, Hidalgo J, Bolea I, Ramirez B, Anglés N, Reguant J, Morelló JR, Gutiérrez C, Boada M, Unzeta M. A diet enriched in polyphenols and polyunsaturated fatty acids, LMN diet, induces neurogenesis in the subventricular zone and hippocampus of adult mouse brain. J Alzheimers Dis 2009; 18:849-65.
57. Niedermeyer E, Ghigo JO. Alzheimer dementia: an overview and a promising new concept. Am J Electroneurodiagnostic Technol 2011;51:82-91.
58. Viola P, Viola M. Virgin olive oil as a fundamental nutritional component and skin protector. Clin Dermatol. 2009; 27:159-65
59. Alcaín FJ, Villalba JM. Sirtuin activators. Expert Opinion on Therapeutic Patents 2009; 19:403–14.
60. Calleja-Agius J, Muscat-Baron Y, Brincat MP. Skin ageing. Menopause Int 2007; 13:60-4.
61. Schlicker C, Boanca G, Lakshminarasimhan M, Steegborn C. Structure-based development of novel sirtuin inhibitors. Aging (Albany NY) 2011; 3:852-72.
62. Lagouge M, Argmann C, Gerhart-Hines Z. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 2006; 127:1109–22.
63. Reddy MA, Jain N, Yada D, Kishore C, Vangala JR, P Surendra R, Addlagatta A, Kalivendi SV, Sreedhar B. Design and synthesis of resveratrol-based nitrovinylstilbenes as antimitotic agents. J Med Chem 2011; 54:6751-60.
64. Saha SS, Ghosh M. Antioxidant effect of vegetable oils containing conjugated linolenic acid isomers against induced tissue lipid peroxidation and inflammation in rat model. Chem Biol Interact 2011; 190:109-20.
65. Kanda N, Mitsui H, Watanabe S. Prostaglandin E(2) suppresses CCL27 production through EP2 and EP3 receptors in human keratinocytes. J Allergy Clin Immunol 2004; 114:1403-9.
66. Verallo-Rowell VM, Dillague KM, Syah-Tjundawan BS. Novel antibacterial and emollient effects of coconut and virgin olive oils in adult atopic dermatitis. Dermatitis 2008; 19:308-15.
67. Gerberick F, Vassallo J, Bailey R, Morrall S, Lepoittevin JP. Development of peptide reactivity assay for screening allergens. Toxicol Sci 2004; 81:332-43.
68. Lodén M, Andersson AC, Effect of topically applied lipids on surfactany-irritated skin. Br J Dermatol 1996; 134:215-20.
69. Docherty JJ, Smith JS, Fu MM, Stoner T, Booth T. Effect of topically applied resveratrol on cutaneous herpes simplex virus infections in hairless mice. Antiviral Research 2004; 61:19–26.
70. Docherty JJ, Sweet TJ, Bailey E, Faith SA, Booth T. Resveratrol inhibition of varicella-zoster virus replication in vitro. Antiviral Research 2006; 72:171–7.
71. Yoon JH, Baek SJ. Molecular targets of dietary polyphenols with anti-inflammatory properties. Yonsei Med J 2005; 46:585-96.
72. Durham PL, Vause CV, Derosier F, McDonald S, Cady R, Martin V. Changes in salivary prostaglandin levels during menstrual migraine with associated dysmenorrhea. Headache 2010; 50:844-51.
73. Cicerale, S., Conlan, X. A., Sinclair, A. J., & Keast, R. S. J. Chemistry and health of olive oil phenolics. Critical Reviews in Food Science and Nutrition 2009; 49:218-36.
74. Kutteh WH, Chao CH, Ritter JO, et al. Vaginal lubricants for the infertile couple: effect on sperm activity. Int J Fertil Menopausal Stud 1996; 41:400-4.

75. Santiago-Mora R, Casado-Díaz A, De Castro MD, et al. Oleuropein enhances osteoblastogenesis and inhibits adipogenesis: the effect on differentiation in stem cells derived from bone marrow. Osteoporos Int 2011; 22:675-84.
76. Kontogianni MD, Melistas L, Yanakoulia M et al. Association between dietary patterns and indices of bone mass in a sample of Mediterranean women. Nutrition 2009; 25:165-71.
77. Rowe S, Alexander N, Almeida NG, et al. Translating the Dietary Guidelines for Americans 2010 to bring about real behaviour change. J Am Diet Assoc 2011; 111:28-39.
78. Verbanac D. Nutrition habits in pregnant women and early childhood as a tool for obesity prevention. Paediatria Croatica 2004; 48:41-5.

Biofenoli maslinovog ulja i zdravlje žene

Ivan Fistonić[1], Mirna Šitum[2], Vedrana Bulat[2], Mario Harapin[3], Nikola Fistonić[4], Donatella Verbanac[5]

[1]Ordinacija za ginekologiju, porodništvo i perimenopauzu, [2]Klinika za kožne i spolne bolesti, KBC ž'Sestre milosrdnice'', [3]Hrvatski radio, [4]Medicinski fakultet Sveučilišta u Zagrebu, [5]Centar za translacijska i klinička istraživanja, Odjel za međustaničnu komunikaciju, Medicinski fakultet Sveučilišta u Zagrebu; Zagreb, Hrvatska

SAŽETAK

Olea europea, odnosno maslina, je drevno stablo koje je poteklo iz mediteranskog okruženja Male Azije. Plod masline nije samo kulinarski dodatak; maslinovo ulje, produkt njena tlačenja, sadrži cijeli niz dobrobiti po zdravlje. Djevičansko maslinovo ulje je prirodni sok masline, tekući je i najvažniji dio zdravstveno potvrđene mediteranske dijete. Njena pomoć zdravlju izvire iz biofenola i skvalena (oleokantal, tirozol, hidroksitirozol, oleuropein). Oni pružaju izuzetnu protuoksidativnu aktivnost uklanjajući iz organizma štetne spojeve koji narušavaju zdravlje. Oksidansi leže u temeljima mnogih bolesti i stanja - srčanožilnih, malignih, osteoporoze, Altzheimerove bolesti, predmenstrualnog sindroma. Nezasićena oleinska masna kiselina pokazala je značajan učinak u prevenciji zloćudnih bolesti, primjerice raka debelog crijeva i raka dojke, a biofenoli maslinovog ulja uspješno suzbijaju sintezu LDL-a, bjelančevine koja je ključna u nastanku krvnožilnih bolesti, smanjujući krvni tlak i nastanak aterosklerotskog plaka.

Ključne riječi: maslinovo ulje, biofenoli, zdravlje

REVIEW

Role of laparoscopic surgery in treatment of infertility

Siniša Šijanović[1, 2], Domagoj Vidosavljević[3], Ivanka Šijanović[4]

[1]Department of Gynaecology and Obstetrics , J.J. Strossmeyer University School of Medicine Osijek, [2]Department for Minimally Invasive Gynaecology, Clinic of Gynaecology and Obstetrics, Clinical University Center of Osijek; Osijek, [3]Department of Gynaecology and Obstetrics, Vukovar General Hospital, Vukovar, [4]Department of Ophthalmology, Vukovar General Hospital, Vukovar; Croatia

ABSTRACT

The role of laparoscopy in assisted reproduction is disputed by many. A rising problem of infertility is battled by an increasing number of centres for reproductive medicine in the region. Nevertheless, there is a large number of indications and conditions where laparoscopic surgery should not be avoided as a therapeutic choice or an aid in assisted reproductive techniques (ART).

The number of centres where laparoscopic surgery is performed is significantly higher than the number of reproductive centres; a number of gynaecologists educated in laparoscopic gynaecology is growing, making it more available for patients.

Key words: assisted reproductive technique, infertility, laparoscopic surgery

Corresponding author:
Siniša Šijanović
Department for Minimally Invasive Gynaecology, Clinic for Gynaecology and Obstetrics,
Clinical University Centre of Osijek
J. Huttlera 4 , 31000 Osijek, Croatia
Phone: +385 31 502 344;
fax: +385 31 512 307;
E-mail: sinisa.sijanovic@os.htnet.hr

Original submission:
27 March 2011;
Revised submission:
07 June 2011;
Accepted:
04 July 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):10-16

INTRODUCTION

The role of laparoscopy in diagnostics and treatment of infertility has its place, although there are many disputes among different authors. Diagnostic laparoscopy is used by 87 % of reproductive gynaecologists in the United States as a method of choice in diagnostics of infertility (1). On the other hand, some authors claim that only 40-70% of pelvic pathology , especially minimal and mild endometriosis, is discovered when diagnostic laparoscopy is used (2).

The role of diagnostic laparoscopy in diagnostics of infertility is based on two major issues.

First of all, is it necessary to perform diagnostic laparoscopy as a final method with possible conversion to therapeutic mode and with the effect that reproductive surgery has to pregnancy rate?

Second, is laparoscopy indicated after many unsuccessful inductions of ovulation or artificial reproductive techniques (ART) in order to enhance pregnancy rate?

Nowadays, with technological improvements and increasing number of IVF centres diagnostic laparoscopy is avoided as method due to possible surgical complications and risk of general anaesthesia (3).

Although minimally invasive, endoscopy is still invasive diagnostic and therapeutic method that carries a risk of possible surgical complications, although minimal, but still possible anaesthesiologic complications, adhesions, and patients fear of surgery as such; and adhesions after laparoscopic procedures are minimal, less than by laparotomy (4).

On the other hand it has great advantages - in hands of a skilful surgeon operation that starts as a diagnostic procedure can be easily transformed into therapeutic reproductive surgery. There is also a possibility of hysteroscopic evaluation of uterine cavity resolving any intrauterine pathology (5). Most endoscopic centres in the world do one-day-surgeries, while office hysteroscopy takes more place in reproductive surgery (6).

DIAGNOSTIC LAPAROSCOPY VS. HYSTEROSALPINGOGRAPHY OR HYSTEROSALPINGO-CONTRAST-SONOGRAPHY

Hysterosalpinography (HSG) enables morphological overview of uterine cavity, salpinx and their conductivity. HSG has reasonable specificity of 83% but bad sensitivity of 65% (7). It gives 50-90% of false negative results and 30-80% of false positive results (8). The method can also have adverse effects such as lower abdominal pain that occurs when contrast is injected, patients' discomfort, and it is one of the most painful procedures in gynaecology. It can also induce an exacerbation of pelvic inflammatory disease, tuboovarian abscess and pelveoperitonitis (9)

Hysterosalpinography plays no role in diagnostics of endometriosis. X-ray can have bad influence on unrecognized pregnancy so it has to be performed in the first half of the menstrual cycle. A comparison of 18th month cumulative pregnancy rate shows no difference between diagnostic laparoscopy (DL) and HSG (8).

A Slovenian study describes pathological findings in 79 % of patients that underwent DL: in 46% of patients tuboovarial adhesions were found, in 27 % of cases endometriosis was found. At the same time sensitivity of HSG was 68 %. Slovenian authors concluded that laparoscopy as a diagnostic method in infertile patients has important diagnostic and therapeutic role, while HSG as a method has only limited diagnostic value (10).

Retrospective analysis of patients treated at the University Hospital of Osijek has also shown that pathological findings were present in 77 % of patients treated for infertility . Out of that number 28 % of cases were tuboovarial adhesions and 21% of cases were female patients with endometriosis. Findings and conclusions in our study were similar as those represented in the Slovenian study (11).

Hysterosalpingo-Contrast-Sonography (Hy-Co-Sy) is an attractive alternative to HSG because patients are not exposed to X ray or iodine contrast. There is a strong similarity in results between HSG and HyCoSy (12).

TUBOPERITONEAL PATHOLOGY

Prevalence of peritubal adhesions in infertile patients is between 10-23% (13).

Positive anamnestic data of previous pelvic inflammatory disease (PID), abnormal vaginal excretion or previous genital and urinal tract infections are indicators of tuboperitoneal pathology (14). Presence of Chlamydial antibodies is an indicator

of early stage Chlamydial infection, as the most important etiological factor in the development of pelvic inflammatory disease (2). It is believed that 25 % of infertile patients have a tubal factor as a cause of infertility (14).

Phymosis of abdominal ostia, proximal and distal occlusion can now be easily differentiated.

Diagnostic laparoscopy of tubal lesions can be easily continued as therapeutic (5) .

Tuboovarial adhesions, tubal occlusion and hydrosalpinx occur most frequently as a consequence of PID (15). Pelvic inflammatory disease occurs in 85 % of cases after sexually transmitted diseases-adhesions in the pelvic region as a result of chronic inflammation are multiple damaging factors for reproductive capacity of a female (16).

Johnson et al. conducted two Cochrane systematic reviews recommending laparoscopic salpingectomy before the IVF procedure, making unilateral or bilateral surgery, depending on the extension of the process, after which probability of intrauterine pregnancies rises up to 95 % (15,17).

They also recommend that salpingostomy be considered if damage is of smaller or medium grade. The treatment outcome in salpingostomy is defined by successful intrauterine pregnancy rate of 33-42% and extra uterine pregnancy rate of 7%. In case of phimosis of abdominal orifice, deglutination of fimbriae or fimbrioplasty is performed.

But in 2010 report, Johnson leaves a possibility of laparoscopic tubal agglutination as an alternative to other procedures (15,17).

In case of infertility our primary task is to remove any adhesions that interfere with reproductive physiology (ovulation, transport of oocyte or conceptus) (17).

In cases of chronic pelvic pain it is necessary to remove all possible adhesions and mobilize all pelvic organs . Pelvic adhesions are usually a consequence of pelvic inflammatory diseases, endometriosis or surgical procedures (18). Reappearance of adhesions after laparoscopic adhesiolysis can be seen in 12 %, while after laparotomy it can appear in 50 % of patients (19).

ROLE OF LAPAROSCOPY IN TREATMENT OF MINIMAL AND MILD ENDOMETRIOSIS

Prevalence of endometriosis in infertile patients is between 26-68% and is higher than among general population of reproductive age, where prevalence ranges between 2.5-3.3 % (20). Middle and severe stages of endometriosis lead to malformations of normal pelvic topography and damage reproductive function. Minimal and mild endometriosis reduce fertility by other mechanisms including toxic factors in peritoneal fluid which reduces folliculogenesis and luteal function. In stages I and II monthly fecundity rate is approximately 7% (21). Although connection between minimal and mild endometriosis and fertility might be considered coincidental, there are many arguments in favour of the thesis that there is in fact a strong relation between I and II grade endometriosis and infertility (22).

Different stages of pathology and different clinical signs can also demand different levels of interventions. Endometriosis can be considered symptomatic and asymptomatic and by clinical classification it can be divided into endometriosis without palpable lesions (Sampson syndrome) or endometriosis with palpable lesions (Cullen syndrome). Depending on the presence of palpable lesions further preoperative diagnostics and preparations for wider and more extensive surgical procedure will be considered necessary (23).

There is a positive correlation between a level of endometriosis and serum value of tumour marker Ca 125 which can also be considered as a preoperative predictor. One of the modern diagnostic tests is CCR 1 mRNA (chemokine related receptor 1 mRNA) in peripheral blood as a blood test for endometriosis. CCR is a specific receptor for the surface of neutrophiles/mononuclear leukocytes. It is elevated in pregnant women, acute PID and in endometriosis (24).

First randomized study of a Canadian collaboration group compared infertility and endometriosis. In the first group laparoscopic resection or ablation was performed in minimal and mild endometriosis, while in the second group only a diagnostical laparoscopy was performed. The first group had the pregnancy rate of 31 %, while the second group had pregnancy rate of 18% (25).

The European Society for Human Reproduction and Endocrinology (ESHRE), special group for endometriosis recommended in its guidelines surgical treatment of minimal and mild endometriosis in infertile women (26).

Garry concluded that laparoscopic excision of endometriomas significantly reduced all aspects of pelvic pain, improved the quality of life and sexual function in endometriotic women, with successful pregnancy rate of 59% (23). Donnez et al concluded that laparoscopic laser vaporization of endometriotic nodes was a better option in keeping the residual tissue of ovaries. Stripping of endometriomas causes cortical bleeding in hilus and requires extensive coagulation thus leading to the loss of viable cortex, damage to the ovaries and results in lower pregnancy rate (27). Fenestration itself is not considered efficient because it leads to quick renewal and reappearance of endometriosis (28).

In patients with diagnosed rectovaginal endometriosis Keckstein et al. concluded that radical laparoscopic excision and segmental resection with frontal anastomosis reduce chronic pelvic pain in 96% of patients, improve sexual activity in 88%, reduce dispareunia in 87% with pregnancy rate of 50% (29).

Some recent published reports suggest that patients with ultrasound confirmation of ovarian endometriosis should be confined to IVF without surgery, since the presence of ovarian endometrioma does not reduce the number of oocytes and as they conclude, ovarian endometrionas should be removed only in cases if they "stand in way" of oocytes during oocyte aspiration (30).

LAPAROSCOPIC OVARIAN DRILLING (LOD) IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME (PCOS)

Approximately 20% of patients diagnosed with PCOS and infertility do not ovulate after induction of ovulation with clomiphene–citrate. Over 20 years ago laparoscopic coagulation of ovarian cortex in clomiphene resistant PCOS patient was described with 92% ovulation rate and 69% pregnancy rate (31). Disadvantages of LOD are general risks of surgical procedure, need for general anesthesia, possible risk of thermal injury of adjacent organs as well as the lack of knowledge on long term effect on ovarian reproductive physiology; and as such they are cited in Cochrane analysis (32). Advantages of LOD are primarily in a possibility of surgical treatment of another pelvic pathology linked with infertility (peritubal adhesions, endometriosis etc.). Cochrane analysis shows no evidence for the existing difference in a rate of live born children or pregnancy rates among patients treated with LOD or just treated with gonadotropins . On the other hand, multiple pregnancy rate was significantly lower in LOD treated patients in comparison with the group treated with gonadotropins (32) and pregnancies had less complications than those compared to clomiphene or metformine (33).

According to some authors spontaneous ovulations after LOD occur in 73%, and the cumulative pregnancy rate after 12 months is 54 %, so they have concluded that LOD is an efficient method of treatment in clomiphene resistant anovulatory patients with PCOS (34).

It is usually done with a thin monopolar needle, making numerous punctures of ovarian cortex, although it can also be done with the use of small (1 mm) bipolar forceps, as described by Barišić et al with same efficiency but lesser damage to adjacent tissue (35,36).

LAPAROSCOPIC MYOMECTOMY AND INFERTILITY

Italian authors have published by far the largest study of laparoscopic myomectomies on more than 2000 women. Authors included 48% of multiple myomectomies, with myomas ranging between 1 and 20 cm, with complications rate of 11,1% and with one spontaneous rupture of uterus in the 33rd week of pregnancy. Pregnancy rate was 69, 8% (37).

Myomas reduces delivery rate by 30 %, therefore myomectomy is also significant for pregnancy outcome (38).

A German group of authors investigated women who underwent laparoscopic myomectomy for infertility and determined that the pregnancy rate after myomectomy was 46%, with no uterine rupture occurring during birth. They concluded that laparoscopy was associated with fewer postoperative complications and since no preoperative or intraoperative factors seem to influence the fertility outcome in women with uterine myomas, laparoscopy is the treatment of choice in these patients (39).

Laparoscopic myomectomy is a widespread surgical technique in reproductive surgery well accepted in whole of the world (40).

LAPAROSCOPY BEFORE IVF?

Many authors still support alternative diagnostic methods in the diagnostics of tubal pathology in everyday practice, such as HSG and Chlamydial antibodies, although laparoscopy represents the golden standard in the diagnostics of tubal and peritoneal pathology (41). Diagnostic laparoscopy can be avoided in cases of clearly confirmed diagnosis where IVF is considered as only successful treatment (5).

However, many agree that in cases of adnexal pathology such as hydrosalpinx or endometriotic cysts, laparoscopic surgery is needed before IVF procedure (8).

LAPAROSCOPY IN IDIOPATHIC INFERTILITY

Nakagawa et al have studied the use of laparoscopic surgery in patients who were diagnosed with unexplained (idiopathic) infertility, comparing two groups: first those who underwent ART treatment without prior laparoscopy and the second group that underwent laparoscopy before any other ART techniques. They discovered that in 87.2% of the women, laparoscopy revealed abnormal findings; endometriosis lesions, peritubal adhesions and tubal obstructions. After laparoscopy 48.9% of the patients achieved pregnancy, with the pregnancy rates ranging between 27.2 and 100 % according to age groups. Authors recommend that laparoscopy should be strongly considered for examining women with unexplained infertility (42). Another Japanese group of authors has performed laparoscopies in patients with unexplained infertility. In their conclusion, they found no significance in pregnancy rates between patients who underwent IVF or spontaneously achieved pregnancy (43).

AGE OF THE PATIENT AND LAPAROSCOPY

There is general tendency of avoiding laparoscopic treatment in patients older than 35 due to the fact that their reproductive capacity is weakening with age (44). From our clinical experience, we have seen that many women are sent directly to the IVF centers, often with insufficient pretreatment diagnostics (11). The aforementioned studies indicate that there is a significant benefit for patients, if laparoscopy is performed, even in cases of unexplained infertility (42,43).

The issue of ovarian reserve and functional fertile capacity of women can be easily resolved by determination of serum Anti Müllerian Hormone (AMH) level.

Anti-Mullerian hormone is produced by the granulosa cells of the antral and preantral follicles and serum AMH levels reflect the ovarian pool of primordial follicles (44). Anti-Mullerian hormone levels remain stable during adulthood decreasing towards menopause (45),. Inter and intracycle variability of AMH is low enough to allow measurement at any time of the cycle. More importantly, AMH levels are not affected by contraceptive pills or GnRH agonists (46).

Moreover, AMH is a good predictor of ovarian response in younger patients (45) and can also be a predictor of live birth as a result of IVF (47). Furthermore, AMH can be used as a marker of extensiveness of the endometrioma resection by its postoperative decline (48).

The number of centers in our region in which AMH level can be determined is increasing.

In conclusion, the routine use of diagnostic laparoscopy in evaluation of female infertility is still a matter of discussions. Current evidence shows that surgical treatment of minimal and mild endometriosis improves pregnancy rate. The European Society for Human Reproduction and Endocrinology (ESHRE) has recommended in its guidelines IVF as a suitable method of reproduction especially in cases of tubal pathology, severely reduced male fertility and more unsuccessful attempts of assisted reproduction (26), but laparoscopic salpingectomy is indicated before IVF procedure, if a hydrosalpinx is verified by ultrasound (15,17).

The use of laparoscopy in diagnostics and treatment of tubal pathology is known and undisputed.

Diagnostic laparoscopy is indicated in cases of bilateral anomaly seen on HSG.

Role of laparoscopy in cases of unexplained infertility is still a matter of discussions, but some reported studies are in favour of diagnostic laparoscopies (42,43) Laparoscopic ovarian drilling does not have better influence on ovulation in comparison with gonadotropin use, but LOD significantly reduces the risk of multiple pregnancies when compared to gonadotropins, and reduces number of miscarriages and complications

in pregnancy when compared to clomiphene and metformine (32,33,35)

Laparoscopic surgery is an invasive procedure but all practitioners should be aware of all possible benefits and complications of its use. The increasing number of IVF centres in the region is still less than the number of hospitals with gynecologists experienced in laparoscopies, and costs of surgery are still lower than cost of IVF treatment. Laparoscopy has its place in the diagnostics and treatment of infertility with proper indications and with experienced gynecologists.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCE

1. Glatstein IZ, Harlow BL, Hornstein MD. Practice patterns among reproductive endocrinologists: the infertility evaluation. Fertil Steril 1997; 67:443–51.
2. Forman RG, Robinson JN, Mehta Z, Barlow DH. Patient history as a simple predictor of pelvic pathology in subfertile women. Hum Reprod 1993; 8:53–5.
3. 3. Coccia ME Rizzello F, Cammilli F, Bracco GL, Scarselli G. Endometriosis and infertility surgery and ART: An integrated approach for succesfull management. Eur J Obstet Gynecol Reprod Biol. 2008 ;138:54-9
4. Levine RL. Operative laparoscopy.TeLindes Oper Gynecol Updates. 1992;1(3):1-13
5. Ball E, Koh C, Janik G, Davis C. Gynaecological laparoscopy; „see and treat „should be gold standard .Curr Opin Obstet Gynecol 2008; 20:325-30.
6. Brosens I, campo R, Puttemans P, Gordts S. One-stop endoscopy based infertility clinic.Curr Opin Obstet Gynecol 2002; 14:397-400.
7. Swart P, Mol BWJ, van der Veen F, van Beurden M, Redekop WK, Bossuyt PMM. The value of terosalpingography in the diagnosis of tubal pathology, a meta-analysis. Fertil Steril 1995; 64:486–91.
8. Perquin DAM, Do¨rr PJ, de Craen AJM, Helmerhorst FM. Routine use of hysterosalpingography prior to laparoscopy in the fertility workup: a multicentre randomized controlled trial. Hum Reprod 2006; 21:1127–231.
9. Simpson WL, Beitia LG, Mester J. Hysterosalpingography: a reemerging study. Radiographics. 2006; 26:419-31.
10. Bokal VE. Analysis of laparoscopies in infertile patients. In: Book of abstracts. World Congress on Gynecological Endoscopy. Dubrovnik/Croatia, 15.05.2002. American Association for Gynecologic Laparoscopy / Hrvatsko društvo za ginekološku laparoskopiju, Dubrovnik, 2002, p.17.
11. Šijanović S ,Kasač Z, Vidosavljević D, Košuta M, Šimić I, Haj Barakat M . When endoscopic surgery improves the results of IVF? 4th. AAGL international congress on minimally invasive gynaecology. Dubrovnik/Croatia 23-26.6.2010. Book of abstracts. American Association for Gynecologic Laparoscopy / Hrvatsko društvo za ginekološku endoskopiju. Dubrovnik, 2010, pp.25-26.
12. Hamilton J, Hamilton J, Latarche E, Gillott C, Lower A, Grudzinskas JG. Intrauterine insemination results are not affected if Hysterosalpingo Contrast Sonography is used as the sole test of tubal patency. Fertil Steril 2003; 80:165–71.
13. Al Badawi IA, Fluker MR, Bebbington MW. Diagnostic laparoscopy in infertile women with normal hysterosalpingograms. J Reprod Med 1999; 44:953–7.
14. Hubacher D, Grimes D, Lara-Ricalde R, de la Jara J, Garcia-Luna A. The limited clinical usefulness of taking a history in the evaluation of women with tubal factor infertility. Fertil Steril 2004; 81:6–10.
15. Johnson NP, Mak W, Sowter MC. Laparoscopic salpingectomy for women with hydrosalpinges enhances the success of IVF: a Cochrane review. Hum Reprod 2002; 17:543-8.
16. Akande V , Turner C, Horner P, Horne A, Pacey A; British Fertility Society. Impact of Chlamydia trachomatis in the reproductive setting: British Fertility Society Guidelines for practice. Hum Fertil (Camb) 2010 ;13:115-25.
17. Johnson NP, Van Voorst S, Sowter MC, Strandel A, Mol BW. Surgical treatment for tubal disease in women due to undergo in vitro fertilization. Cochrane Database syst review. 2010; CD 002125
18. Neis KJ, Neis F. Chronic pelvic pain; cause, diagnosis and therapy from gynaecologist's and an endoscopist's point of view.Gynecol Endocrinol 2009; 25:757-61.
19. Luciano DE, Roy G, Luciano AA. Adhesion reformation after laparoscopic adhesiolysis: where, what type and in whom are they most likely to recur. J Minim Invasive Gynecol. 2008;15:44-8.
20. Mahmood TA, Templeton A. Prevalence and genesis of endometriosis. Hum Reprod 1991; 6:544–9.
21. Collins A, Burrows EA, Willan AR. The prognosis for live birth among untreated infertile couples. Fertil Steril 1995; 64:22–8.
22. Hondt A, Meuleman C, Tomassetti C, Peeraer K, D'Hooghe TM. Endometriosis and assisted reproduction: the role for reproductive surgery? Curr Opin Obstet Gynecol 2006; 18:374–9.
23. Garry R. The effectiveness of laparoscopic excision of endometriosis. Curr Opin Obstet Gynecol 2004; 16:299-303.
24. Agic A, Xu H, Rehbein M, Wolfler MM, Ebert AD, Hornung D. CCR1 mRNA expression in peripheral blood as a diagnostic test for endometriosis. Fertil Steril 2007; 87:982-4.
25. Marcoux S, Maheux R, Be´rube S, The Canadian Collaborative Group on Endometriosis. Laparoscopic surgery in infertile women with minimal or mild endometriosis. N Engl J Med 1997; 337:217–22.
26. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E. ESHRE guidelines for the diagnosis and treatment of endometriosis. Hum Reprod 2005; 20:2698–704.

27. Donnez J, Wyns C, Nisolle M. Does ovarian surgery for endometriomas impair the ovarian response to gonadotropin? Fertil Steril 2001; 76:662-5.
28. Beretta P, Franchi M, Ghezzi F, Busacca M, Zupi E, Bolis P. Randomized clinical trialof two laparoscopic treatments of endometriomas: cystectomy versus drainage and coagulation. Fertil Steril 1998; 70:1176-80.
29. Keckstein J, Wiesinger H. Deep endometriosis, including intestinal involvement--the interdisciplinary approach. Minim Invasive Ther Allied Technol 2005; 14:160-6.
30. Almog B, Shehata F, Sheizaf B, Tan SL, Tulandi T. Effects of ovarian endometrioma on the number of oocytes retrieved for in vitro fertilization. Fertil Steril 2011; 95:525-7.
31. Gjonnaess H. Polycystic ovarian syndrome treated by ovarian electrocautery through the laparoscope. Fertil Steril 1994; 41:20–5.
32. Farquhar C, Lilford RJ, Marjoribanks J, Vandekerckhove P. Laparoscopic drilling by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. Cochrane Database Syst Rev 2005; 3:CD001122.
33. Ott J, Kurz C, Nouri K, Wirth S, Vytiska-Binstorfer E, Huber J, Mayerhofer K. Pregnancy outcome in women with polycystic ovary syndrome comparing the effects of laparoscopic ovarian drilling and clomiphene citrate stimulation in women pre-treated with metformin: a retrospective study. Reprod Biol Endocrinol 2010; 8:45.
34. Felemban A, Tan SL, Tulandi T. Laparoscopic treatment of polycystic ovaries with insulated needle cautery: a reappraisal. Fertil Steril 2000; 73:266-9.
35. Kaya H, Sezik M, Ozkaya O. Evaluation of a new surgical approach for the treatment of clomiphene citrate-resistant infertility in polycystic ovary syndrome: laparoscopic ovarian multi-needle intervention. J Minim Invasive Gynecol 2005; 12:355-8.
36. Barišić D, Grizelj V, Ćorušić A. Pregnancy following the laparoscopic bipolar electrocoagulation of polycystic ovaries resistant to medicamentous ovulation induction.Eur J Obstet Gynecol Reprod Biol 1999; 83:225-6.
37. Sizzi O, Rossetti A, Malzoni M, Minelli L, La Grotta F, Soranna L, Panunzi S, Spagnolo R, Imperato F, Landi S, Fiaccamento A, Stola E. Italian multicenter study on complications of laparoscopic myomectomy. J Minim Invasive Gynecol 2007; 14:453-62.
38. Ezzati M, Norian JM, Segars JH Management of uterine fibroids in the patient pursuing assisted reproductive technologies. Womens Health (Lond Engl) 2009; 5:413-21.
39. Agdi M, Tulandi T. Minimally invasive approach for myomectomy. Semin Reprod Med 2010; 28:228-34
40. Hackethal A, Westermann A, Tchartchian G, Oehmke F, Tinneberg HR, Muenstedt K, Bojahr B. Laparoscopic myomectomy in patients with uterine myomas associated with infertility. Minim Invasive Ther Allied Technol 2011 (ahead of print).
41. Mol BWJ, Dijkman B, Wertheim P, Lijmer J, van der Veen F, Bossuyt PMM.The accuracy of serum chlamydial antibodies in the diagnosis of tubal pathology: a meta-analysis. Fertil Steril 1997; 67:1031–7.
42. Nakagawa, K, Ohgi S, Horikawa T, Kojima R, Ito M, Saito H Laparoscopy should be strongly considered for women with unexplained infertility. J Obste Gynaecol Res 2007; 33:665–70.
43. Shimizu Y, Yamaguchi W, Takashima A, Kaku S, Kita N, Murakami T. Long-term cumulative pregnancy rate in women with unexplained infertility after laparoscopic surgery followed by in vitro fertilization or in vitro fertilization alone. J Obste Gynaecol Res 2011(ahead of print).
44. George K, Kamath MS. Fertility and age. J Hum Reprod Sci 2010; 3:121-3.
45. La Marca A, Sighinolfi G, Radi D, Argento C, Baraldi E, Artenisio AC. Anti Mullerian hormone as a predictive marker in assisted reproductive technology (ART). Hum Reprod Update 2010; 16:113-30.
46. Barad H, Weghofer A, Gleicher N. Utility of age-specific serum anti-Müllerian hormone concentrations. Reprod Biomed Online 2011; 22:284-91.
47. La Marca A, Nelson SM, Sighinolfi G, Manno M, Baraldi E, Roli L, Xella S, Marsella T, Tagliasacchi D, D'Amico R, Volpe A. Anti-Müllerian hormone-based prediction model for a live birth in assisted reproduction. Reprod Biomed Online 2011 (ahead of print).
48. Hirokawa M, Iwase A, Goto M, Takikawa S, Nagatomo Y, Nakahara T, Bayasula B, Nakamura T, Manabe S, Kikkawa F. The post-operative decline in serum anti-Mullerian hormone correlates with the bilaterality and severity of endometriosis. Hum Reprod 2011; 26:90

Uloga laparoskopije u liječenju neplodnosti

Siniša Šijanović[1, 2], Domagoj Vidosavljević[3], Ivanka Šijanović[4]

[1]Katedra za ginekologiju i porodništvo Medicinskog fakulteta Sveučilišta ž'J. J. Strossmeyer'', Osijek, [2]Klinika za ginekologiju, KBC Osijek; Osijek; [3]Odjel za ženske bolesti i porodništvo, Opća bolnica Vukovar, [4]Očni odjel, Opća bolnica Vukovar; Hrvatska

SAŽETAK

Uloga laparoskopije u medicinski potpomognutoj oplodnji osporavana je od strane mnogih stručnjaka. Rastući problem neplodnosti se pokušava suzbiti povećanjem broja centara za reproduktivnu medicinu u regiji. Još uvijek postoji veliki broj indikacija i stanja u kojima endoskopska kirurgija ne bi trebala biti izbjegavana kao terapijski izbor ili potpora metodama medicinski potpomognute oplodnje. Broj centara u kojima se izvodi endoskopska kirurgija značajno je veći od broja reproduktivnih centara, a broj ginekologa educiranih u endoskopskoj ginekologiji raste, što je čini dostupnijom metodom za pacijentice.

Ključne riječi: neplodnost, laparoskopska kirurgija, potpomognuta oplodnja

REVIEW

Starch for health

Drago Šubarić[1], Đurđica Ačkar[1], Jurislav Babić[1], Borislav Miličević[2]

[1]Faculty of Food Technology, Osijek, [2]Zvečevo d. d. Food Industry, Požega; Croatia

ABSTRACT

It is well established that part of starch is resistant to human amylases and escapes undigested to large bowel. This fraction of starch is resistant starch. Recent studies have shown that resistant starch may be a substrate for bacterial flora of the colon and serves as prebiotic. Short chain fatty acids (SCFA) produced by colonic fermentation of resistant starch may have impact on colonic function and health of humans. This paper summarises current knowledge on properties and health impact of resistant starch.

Keywords: resistant starch, prebiotic, SCFA

Corresponding author:
Đurđica Ačkar
Faculty of Food Technology,
University of Josip Juraj Strossmayer,
Osijek
Kuhačeva 20, 31000 Osijek, Croatia
Phone: +385 31 224 300;
fax.: +385 31 207 115;
E-mail: dackar@ptfos.hr

Original submission:
01 April 2011;
Revised submission:
25 August 2011;
Accepted:
07. September 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):17-22

INTRODUCTION

Human nutrition is the provision to humans to obtain materials necessary to support life. Nowadays, food is not seen only as a source of energy, but as a tool for maintaining good health. Namely, it is well established that complex carbohydrates – dietary fibre and resistant starch have a beneficial effect on digestion and contribute to bowel health.

Since typical Western diet is characterised by low intake of fresh fruit and vegetables and high intake of refined foods rich in saturated fats and simple carbohydrates, dietary fibre intake is inadequate (1). Therefore, food industry is directing new product development towards products with increased content of dietary fibre. Since dietary fibres bond high portion of water and impart texture and taste of bakery products, their application in food industry is limited. Therefore, there is increasing research on resistant starch properties, its impact on human health and potentiality of its usage in functional food products.

STARCH

Starch granules contain two principal types of polysaccharides: amylose and amylopectin (2, 3). Both of these are polymers of solely α-D-glucose. Amylose is predominantly linear polymer in which glucose units are bound by α-1,4-glycosidic bonds. In fact, branching points (α-1,6-glycosidic bonds) do exist, but they are rare and amylose has properties of linear polymer, mainly helical structure (4). Inside the helix, molecules of water are often incorporated.

On the other hand, amylopectin is highly branched polymer with glucose units linked by α-1,4-glycosidic bonds in linear chains and α-1,6-bonds on numerous branching points. It is partially crystallite polymer with alternate crystallite regions and amorphous zones combined into clusters (5).

Amylose and amylopectin are radially organised into starch granules, whose size and shape depend on botanical origin.

Starch digestion

Starch is the only food polysaccharide occurring naturally which can be digested by the intrinsic enzymes of the human gastro-intestinal tract (6). Starch digestion begins in the mouth. Food is broken into smaller pieces by chewing and saliva moistens the food. α-amylase, an enzyme in saliva, begins to break down starch to oligosaccharides and maltose. Tongue shapes the food into bolus which is swallowed and transported to the stomach. Low pH in the stomach (close to 1) inhibits enzyme activity and therefore starch does not break down further until it reaches small intestine. In the small intestine, starch is finally broken down to glucose and maltose by action of pancreatic amylase (7, 8). Glucose is absorbed in the small intestine by active transport and passive diffusion through villi (9).

However, not all starch is hydrolysed and absorbed in small intestine (7). Enzymatic digestion of starch can be affected by granule structure, presence of lipids, proteins and minerals, amylose to amylopectin ratio, digestion conditions and particle size (10, 11). In addition, digestion of starch in small intestine is influenced by food preparation which can attribute to starch retrogradation (12, 13) as well as by physiological factors, such as chewing, bowel movement and menstrual cycle in women (14).

Part of starch escapes digestion in small intestine and may be fermented in large intestine by intestinal microflora (15). Based on the action of enzymes, starch can be classified into three categories:

1. Rapidly digestible starch (RDS). RDS is digested in 20 minutes, and is present in cooked starchy food, such as mashed potatoes.
2. Slowly digestible starch (SDS). Digestion of this type of starch is full, but much slower than of RDS (20 min to 1 hr). SDS consists of physically inaccessible amorphous starch, raw starch (cereals) and retrograded starch in cooked foods (potato salad).
3. Resistant starch (RS). This type of starch is not digested even after 120 minutes. The popular definition of RS is “starch (and starch derivatives) that escapes digestion in small intestine and undergoes fermentation in large intestine” (16).

Types and properties of resistant starch

Resistant starch (RS) resists digestion in small intestine for different reasons. Therefore, it is subdivided into four categories: RS1, RS2, RS3 and RS4.

Resistant starch type 1 (RS1) is starch entrapped into indigestible wall of partly milled grains and cereals which is physically inaccessible to enzymes. It is thermally stable and can be used as ingredient in wide variety of conventional foods. Chemically, it is determined as difference of glucose released by enzymatic hydrolysis of homogenised and non-homogenised food sample (16).

Resistant starch type 2 (RS2) is starch that resists enzyme digestion due to its compact, dense structure. This is "raw starch" which does not contain water, present in green bananas, raw potato, and high amylose starch. Enzymes have limited access to bonds they hydrolyse and starch is not digested. Chemically, this starch is represented by difference of glucose liberated by enzymatic digestion of cooked, homogenised food sample and sample of raw, non-homogenised food (16).

Resistant starch type 3 (RS3) is a common type of resistant starch, and is mainly retrograded amylose formed during cooling of gelatinised starch. This type of RS is present in all cooked starchy foods (16). During cooking, starch granule is completely hydrated and amylose molecules leach out of the granules. Cooling gelatinised starch causes re-grouping of amylose molecules into double helices which, by further retrogradation, form hexagonal units. For RS3 to be formed, amylose molecules have to have degree of polymerisation (DP) from 10 to 100. Amylose retrogradation is interfered by amylopectin molecules, and can be enhanced by linearization of amylopectin by pullulunase. In addition, retrogradation is influenced by gelatinisation temperature, storage temperature, water content etc. (17).

Chemically, RS3 is starch fraction that degrades neither by cooking nor enzymatic activity. It is soluble only in KOH or DMSO (dimethylsulphoxide) and is completely resistant to gastric amylase (16).

Resistant starch type 4 (RS4) is chemically modified starch, where, in addition to α-1,4 and α-1,6 glycosidic bonds, new chemical bonds occur, e.g. starch phosphates. For commercial RS production, high amylose starches are most suitable (16).

HEALTH IMPACT OF RESISTANT STARCH

It is estimated that intake of RS in developing countries averages between 30 and 40 g/day, while in the EU it is between 3 and 6 g/day (18) and in the USA it averages between 3 and 8 g/day (19). As mentioned above, resistant starch is fermented in large bowel by colonic microflora. Products of fermentation are hydrogen (20), methane and short-chain fatty acids (SCFA), mainly acetic, propionic and butyric acid, with reported increase of butyrate production in humans (21) and rats (18, 22) and increase of acetate concentration in pigs after RS3 consumption (18). Ahmed et al. (2000) reported significant increase of SCFA production in large intestine after RS consumption (23). These SCFAs have positive impact on colonic function and health (24-27). They stimulate colonic muscles, enhance calcium, magnesium and water absorption, and have positive impact on colonic microflora (27-29).

In vivo, SCFAs are absorbed both by diffusion of protonated SCFAs and anion exchange across apical membrane. Butirate is mainly metabolised by colonocites (24), while majority of propionic acid produced in the colon is absorbed and metabolized by the liver (30). Acetate is utilised in synthesis of long chain fatty acids, glutamine, glutamate and ß-hydroxybutyrate (24).

It has been reported that propionic acid has fatty acid lowering effect in animals and humans and could improve insulin sensitivity (30). In addition, SCFAs lower pH of bowel content, which leads to ionisation of potentially cytotoxic compounds including biogenic amines and ammonia and prevents overgrowth of potentially pathogenic bacteria *in vitro* (21). However, role of SCFAs in treatment of diversion colitis or ulcerative colitis was not clearly established due to discrepancies in research results (24).

Influence of RS on faecal bulking is not significant (14, 31, 32), although it has been reported (34). Lopez et al (2000) reported that research on rats showed that RS consumption increased mineral (Ca, Mg, Zn, Fe, Mn, Cu) absorption in large intestine (35). However, De Schrijver et al. (1999) reported that overall mineral absorption was not significantly influenced after consumption of high amylose starch as source of RS, due to decrease of absorption in illeal region which counteracted increase of absorption in the large intestine (33).

Resistant starch promoted growth of intestinal bacteria in rats and could have beneficial effect on inflammatory bowel diseases (36). In addition,

effect of RS from corn or rice on blood glucose and insuline levels, colonic events and hypolipidemic actions and humoral immune responses in Sprague-Dawley streptozotocin-induced diabetic rats was investigated (37). The results showed no significant effect of RS on blood glucose and insuline, but intestinal transit time was significantly shortened and plasma total lipid and both blood and liver cholesterol concentrations were lowered. RS consumption resulted in non-esterified fatty acid and 3-hydroxybutyrate levels suppression 5 h after meal tolerance test (38).

Yamada et al.(2005) reported that bread containing RS significantly inhibited postprandial increase in glucose in adults with fasting blood glucose level between 100 and 140 mg/dL in comparison with bread without RS (39) and Sands et al. (2009) reported that consumption of slowly digesting waxy maize starch leads to blunted plasma glucose and insulin response (40). Al-Tamimi et al. (2010) reported that substitution of standard starch with RS4 attenuated postprandial glucose and insulin levels in normoglycemic humans, although available carbohydrate amount in the food was not changed (41). However, their study did not provide information whether this was due to dietary fibre and/or RS aspects of consumed food.

In addition, Robertson et al. (2003) reported that replacement of "refined flour" with "high RS flour" could improve postprandial insulin sensitivity in normal healthy subjects due to increased rate of colonic fermentation. However, they reported that difference in insulin levels noted were likely to be due to an increase in hepatic internalization of insulin rather than to differences in insulin secretion. They also observed lowering of plasma glucose concentration despite the higher level of insulin clearance and lower circulating insulin levels. This phenomenon was partly attributed to high portal concentration of propionate which has insulin-like effects, stimulating glycolysis, activating glycogen synthase in isolated hepatocytes and reducing gluconeogenesis (38).

These researches indicate that RS could have beneficial impact on prevention of type II diabetes and cardiovascular diseases, where RS1 is most effective of all RS types (42). In addition, ingesting low-glycemic hydrothermally modified starch before cycling exercise blunted the initial spike in serum glucose and insulin and preserved a short burst maximal performance measurement after prolonged cycling bout in adult male cyclists (43).

RS stimulates growth of *Bifidobacterium, Lactobacillus, Eubacterium, Bacteroides*, *Enterobacter* and *Streptococcus* (6, 31, 27, 44-46) and inhibits growth of *Escherichia coli, Clostridium difficile* and sulphur- and sulphate-reducing bacteria, and enhances mucosa regeneration. This is supported by research on recovery time needed for children with cholera induced diarrhoea and other types of infectious diarrhoea. These children recovered much easier when RS (as high-amylose starch) was added to the usual therapy (6).

RS could have role in prevention of colon cancer, since fermentation of RS in large intestine results in large quantity of butyrate, which is even higher than amount of butyrate produced by fermentation of dietary fibre (47). Butiric acid inhibits oxidative stress (48) and malignant transformation of large intestinal epithelial cells (6, 49), and stimulates apoptosis, differentiation of cancer cells (47). It also regulates expression of proteins involved in cellular dedifferentiation in various tumor cells in culture (50). Beneficial effect of butyric acid is supported by low incidence of colon cancer in developing countries, where high quantities of carbohydrate foods are consumed. For instance, in Gambia, where incidence of colon cancer is very low, mean daily intakes of starch by adult men are 375 g. In Madras, India rice is staple food and colon cancer incidence is very low: 1.5/100 000 (47). Research conducted on 1,2-dimethylhydrazine treated Sprague-Dawley rats showed that replacement of digestible starch with resistant starch type 3 (RS3) prevent colon carcinogenesis. This effect was indeed mediated by enhanced apoptosis of damaged cells and changes in parameters of dedifferentiation in colonic mucosa (50).

This effect is even more pronounced when RS is consumed in combination with insoluble dietary fibres (e.g. wheat bran). Namely, RS is rapidly fermented in proximal colon, and colon cancer, as well as inflammatory bowel diseases, mainly occurs in distal colon. Insoluble fibres shift fermentation of RS to the distal bowel and enhance positive effect of RS (51).

In conclusion, health properties of resistant starch have been extensively researched. It is well established that resistant starch has properties of

both soluble and insoluble fibres and improves function of colonic bacteria. However, its impact on glucose and insulin levels, metabolism of fatty acids and bowel cancer requires additional research on both healthy and unhealthy individuals. Additionally, some of the results are quite ambiguous and there is need for standardization of test methods which are being used.

FUNDING

This work was supported by the Ministry of Science, Education and Sports of the Republic of Croatia from scientific project "Development of new modified starches and their application in food industry" No 113-1130473-0571.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Kanosky SE, Davidson TL. Western diet consumption and cognitive impairment: links to hippocampal dysfunction and obesity. Physiol Behav 2011; 103: 59-68.
2. Eliasson AC: Starch in Food. Cambridge: Woodhead Publishing Ltd., 2004.
3. BeMiller JN, Whistler RL. Carbohydrates. In: Fennema OR, ed. Food Chemistry. New York: Marcel-Dekker, Inc., 1996: 191 – 204.
4. BeMiller JN, Whistler RL. Starch: Chemistry & Technology, 3rd ed. Academic Press, 2009.
5. Biliaderis CG. Structures and phase transitions of starch polymers. In: Walter RH, ed. Polysaccharide Association Structures in Food. New York: Marcel Dekker, 1998: 57 – 168.
6. Topping DL, Fukushima M, Bird AR. Resistant starch as a prebiotic and synbiotic: state of art. Proceedings of the Nutrition Society 2003; 62: 171-6.
7. Perera A, Meda V, Tyler RT. Resistant starch: a review of analytical protocols for determining resistant starch and of factors affecting the resistant starch content of foods. Food Res Int 2010; 43: 1959-74.
8. Singh J, Dartois A, Kaur L. Starch digestibility in food matrix: a review. Trends Food Sci Technol 2010; 21: 168-80.
9. Schlenker ED. Carbohydrates. In: Williams SR, Schlenker ED, eds. Essentials of Nutrition & Diet Therapy. Elsevier Health Sciences, 2003.
10. Al-Rabadi GJS, Gilbert RG, Gidley JM. Effect of particle size on kinetics of starch digestion in milled barley and sorghum grains by porcine alpha-amylase. J Cereal Sci 2009; 50: 198-204.
11. Leeman M, Karlsson ME, Eliasson AC, Bjorck IME. Resistant starch formation in temperature treated potato starches varying in amylose/amylopectin ratio. Carb Polym 2006; 65: 306-13.
12. Cummings JH, Edmond LM, Magee EA. Dietary carbohydrates and health: do we still need a fibre concept?. Clinical Nutrition Supplements 2004; 1: 5-17.
13. Alsaffar AA. Effect of thermal processing and storage on digestibility of starch in whole wheat grains. J Cereal Sci 2010; 52: 480-5.
14. Topping DL, Cliffton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and non-starch polysaccharides. Physiol Rev 2001; 81: 1031-64.
15. Zhang W, Bi J, Yan X, Wang H, Zhu C, Wang J, Wan J. *In vitro* measurement of resistant starch of cooked milled rice and physic-chemical characteristics affecting its formation. Food Chem 2007; 105: 462-8.
16. Sajilata MG, Singhal RS, Kulkarni PR: Resistant starch – A Review. Compr Rev Food Sci Food Saf 2006; 5: 1-17.
17. Garcia-Alonso A, Jimenez-Escrig A, Martin-Carron N, Bravo L, Saura-Calixto F. Assessement of some parameters involved in the gelatinisation and retrogradation of starch. Food Chem 1999; 66: 181-7.
18. Nugent A. Health properties of resistant starch. Nutrition Bulletin 2005; 30: 27-54.
19. Murphy MM, Douglas JS, Birkett A. Resistant starch intakes in the United States. J Am Diet Assoc 2008; 108: 67-78.
20. Heacock PM, Hertzler SR, Wolf B. The glycemic, insulinemic, and breath hydrogen responses in humans to a food starch esterified by 1-octenyl succinic anhydride. Nutr Res 2004; 24: 581–92.
21. Topping DL. Cereal complex carbohydrates and their contribution to human health. J Cereal Sci 2007; 220-9.
22. Henningsson AM, Nyman EMGL, Bjork IME. Short chain fatty acid content in the hindgut of rats fed various composite foods and commercial dietary fibre fractions from similar sources. J Sci Food Agric 2002; 82: 385-93.
23. Ahmed R, Segal I, Hassan H. Fermentation of dietary starch in humans. The American Journal of Gastroenterology 2000; 95 (suppl 4): 1017-20.
24. Cook SI, Sellin JH. Review article: short chain fatty acids in health and disease. Aliment Pharmacol Ther 1998; 12: 499-507.
25. Cresci A, Orpianesi C, Silvi S, Mastrandrea V, Dolara P. The effect of sucrose or starch-based diet on short chain fatty acids and faecal microflora in rats. J Appl Microbiol 1999; 86: 245-50.
26. Schwiertz A, Lehmann U, Jacobasch G, Blaut M. Influence of resistant starch on the SCFA production and cell counts of butyrate-producing Eubacterium spp. in the human intestine. J Appl Microbiol 2002; 93: 157–62.
27. Wang X, Brown IL, Khaled D, Mahoney MC, Evans AJ, Conway PL. Manipulation of colonic bacteria and volatile fatty acid production by dietary high amylose maize (amylomaize) starch granules. J Appl Microbiol 2002; 93: 390–7.
28. Jenkins DJA, Kendall CWC. Resistant starches. Curr Opin Gastroenterol 2000; 16: 178-83.
29. Annison G, Illman RJ, Topping DL. Acetylated, Propionylated or Butyrylated Starches Raise Large Bowel Short-Chain Fatty Acids Preferentially When Fed to Rats. J Nutr 2003; 133: 3523-8.
30. Al-Lahham SH, Peppelenbosch MP, Roelofsen H, Vonk RJ, Venema K. Biological effects of propionic acid in humans; metabolism, potential applications and underlying mechanisms. Biochim Biophys Acta 2010; 1801: 1175-83.

31. Quieroz-Monici K da S, Costa GEA, da Silva N, Reis SMPM, de Oliveira AC. Bifidogenic effect of dietary fiber and resistant starch from leguminous on the intestinal microbiota of rats. Nutrition 2005; 21: 602-8.
32. Williamson C, McKevith B, Theobald HE. Conference report – 5th Nutrition and Health Conference. Nutrition Bulletin 2005; 30: 294-7.
33. De Schrijver R, Vanhoof K, Vande Ginste J. Nutrient utilization in rats and pigs fed enzyme resistant starch. Nutr Res 1999; 19 (suppl 9): 1349-61.
34. Ito T, Saito K, Sugawara M, Mochida K, Nakakuki T. Effect of raw and heat-moisture-treated high-amylose corn starches on the process of digestion it the rat digestive tract. J Sci Food Agric 1999; 79: 1203-7.
35. Lopez HW, Coudray C, Bellanger J, Levrat-Verny MA, Demigne C, Rayssiguier Y, Remesy C. Resistant starch improves mineral assimilation in rats adapted to a wheat bran diet. Nutr Res 2000; 20 (suppl 1): 141-55.
36. Jacobasch G, Schmiedl D, Kruschewski M, Schmel K. Dietary resistant starch and chronic inflammatory bowel diseases. Int J Colorectal Dis 1999; 14: 201-11.
37. Kim WK, Chung MK, Kang NE, Kim MH, Park OJ. Effect of resistant starch from corn or rice on glucose control, colonic events, and blood-lipid concentration in streptozotocin-induced diabetic rats. J Nutr Biochem 2003; 14: 166-72.
38. Robertson MD, Currie JM, Morgan LM, Jewell DP, Frayn KN. Prior short-term consumption of resistant starch enhances postprandial insulin sensitivity in healthy subjects. Diabetologia 2003; 46: 659-65.
39. Yamada Y, Hosoya S, Nishimura S, Tanaka T, Kajimoto Y, Nishimura A, Kajimoto O. Effect of bread containing resistant starch on postprandial blood glucose levels in humans. Biosci Biotechnol Biochem 2005; 69 (suppl 3): 559-66.
40. Sands AL, Leidy HJ, Hamaker BR, Maguire P, Campbell WW. Consumption of slow-digesting waxy maize starch leads to blunted plasma glucose and insulin response but does not influence energy expenditure or appetite in humans. Nutr Res 2009; 29: 383-90.
41. Al-Tamimi EK, Seib PA, Snyder BS, Haub MD. Consumption of cross-linked resistant starch ($RS4_{XL}$) on glucose and insulin responses in humans. J Nutr Metab 2010; 2010: 1-6.
42. Han SH, Chung MJ, Lee SJ, Rhee C. Digestion-resistant fraction from soybean (Glycine max (L.) Merrill) induces hepatic LDL receptor and CYP7A1 expression in apolipoprotein E-deficient mice. J Nutr Biochem 2006; 17: 682-8.
43. Roberts MD, Lockwood C, Dalbo VJ, Volek J, Kerksick CM. Ingestion of high-molecular-weight hydrothermally modified waxy maize starch alters metabolic responses to prolonged exercise in trained cyclists. Nutrition 2011; 27: 659-65.
44. Barczynska R, Jochym K, Slizevska K, Kapusniak J, Libudzisz Z. Effect of citric acid-modified enzyme-resistant dextrin on growth and metabolism of selected strains of probiotic and other intestinal bacteria. J Funct Foods 2010; 2: 126-33.
45. Rodriguez-Cabezas ME, Camuesco D, Arribas B, Garrido-Messa N, Comalada M, Bailon E, Cueto-Sola M, Utrilla P, Guerra-Hernandez E, Perez-Roca C, Galvez J, Zarzuelo A. The combination of fructo-oligosaccharides and resistant starch shows prebiotic additive effects in rats. Clin Nutr 2010; 29 (suppl 6): 832-9.
46. Wang X, Brown IL, Evans AJ, Conway PL. The protective effects of high amylose maize (amylomaize) starch granules on the survival of *Bifidobacterium* spp. In the mouse intestinal tract. J Appl Microbiol 1999; 87: 631-9.
47. Segal I, Edwards CA, Walker ARP. Continuing low colon cancer incidents in African population. Am J Gastroenterol 2000; 95 (suppl 4): 859-60.
48. Hamer HM, Jonkers DMAE, Bast A, Vanhoutvin SALV, Fischer MAJG, Kodde A, Troost FJ, Venema K, Brummer R-JM. Butriate modulates oxidative stress in the colonic mucosa of healthy humans. Clin Nutr 2009; 28: 88-93.
49. Fuentez-Zaragoza E, Riquelme-Navarette MJ, Sanchez-Zapata E, Perez-Alvarez JA. Resistant starch as functional ingredient: a review. Food Res Int 2010; 43: 931-42.
50. Bauer-Marinovic M, Florian S, Muller-Schmehl K, Glatt H, Jacobasch G. Dietary resistant starch type 3 prevents tumor induction by 1,2-dimethylhydrazine and alters proliferation, apoptosis and dedifferentiation in rat colon. Carcinogenesis 2006; 27 (9): 1849-59.
51. Govers MJAP, Gannon NJ, Dunshea FR, Gibson PR, Muir JG. Wheat bran affects the site of fermentation of resistant starch and luminal indexes related to colon cancer risk: a study in pigs. Gut 1999; 45: 840-7.

Škrob za zdravlje

Drago Šubarić[1], Đurđica Ačkar[1], Jurislav Babić[1], Borislav Miličević[2]

[1]Prehrambeno-tehnološki fakultet, Osijek; [2]Zvečevo prehrambena industrija d. d., Požega; Hrvatska

SAŽETAK

Poznato je da je dio škroba otporan na djelovanje amilaza čovjeka, te da neprobavljen odlazi u debelo crijevo. Ovaj dio škroba zove se rezistentni škrob. Novija istraživanja pokazuju kako bi rezistentni škrob mogao imati prebiotička svojstva, odnosno crijevnoj mikroflori služiti kao supstrat za fermentaciju. Rezultat fermentacije su kratkolančane masne kiseline koje mogu imati utjecaj na rad crijeva i zdravlje pojedinca. U ovom radu dat je kratak pregled trenutnih spoznaja o svojstvima rezistentnog škroba i njegovom utjecaju na zdravlje.

Ključne riječi: rezistentni škrob, prebiotik, kratkolančane masne kiseline

REVIEW

Medical applications of wireless sensor networks – current status and future directions

Krešimir Grgić, Drago Žagar, Višnja Križanović

Department of Communications, Faculty of Electrical Engineering, University J. J. Strossmayer, Osijek, Croatia

ABSTRACT

In recent years a significant development of BASN (Body Area Sensor Networks) as a special subclass of WSN (Wireless Sensor Networks) has emerged. These networks have enabled a rapid development of telemedicine systems, which provide remote monitoring of patients and their vital parameters. The article gives a short overview of the BASN networks. Furthermore, a general system architecture of telemedicine systems is proposed. The proposed architecture includes a local sensory area, a communication network area and an institutional network area. It also provides the security and privacy of patient-related data. Furthermore, the article surveys some existing telemedicine systems. Finally, some current problems are explained and the directions for the future development of the telemedicine systems are given.

Key words: wireless, network, sensor, telemedicine

Corresponding author:
Krešimir Grgić
Department of Communications,
Faculty of Electrical Engineering,
University J. J. Strossmayer, Osijek
Kneza Trpimira 2b, 31000 Osijek, Croatia
Phone: +385 224 768;
Fax: +385 224 605;
E-mail: kresimir.grgic@etfos.hr

Original submission:
04 April 2011;
Revised submission:
07 June 2011;
Accepted:
29 June 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):23-31

INTRODUCTION

Significant technological advances in recent years have enabled the development of wireless sensor networks (WSN) as a new technology with wide application possibilities (1, 2). For the development of WSN, the advances in the area of microelectronics, wireless communications, micro-electro-mechanical systems (MEMS) and the sensing technology have been most significant. Such advances have enabled the development of the low-cost miniature intelligent sensor nodes, which are capable of mutual wireless communication. Sensor nodes can be equipped with different sets of nodes, depending on the specific application. Every sensor node is capable of sensing, data processing and wireless communication with neighbouring sensor nodes and/or other devices (e.g. base station). Such sensor networks can be seamlessly integrated in other network structures, such as wireless personal-area (WPAN) or wireless body-area networks (WBAN).

Wireless sensor networks have quickly become a widely adopted technology and found many possible applications (3). Medical applications of the wireless sensor networks are one of the most promising areas for their practical use (4, 5). There are many research efforts worldwide that are focused on the development of the reliable, flexible and inexpensive WBAN network suitable for medical applications (6, 7). Research efforts resulted in certain prototypes of wireless networks specialized for medical applications (8, 9, 10, 11). Some of these prototypes could become accepted and used in practice worldwide.

The authors analyze the current status of the research of medical wireless sensor networks. This paper surveys the current projects and prototypes of this area. The authors also propose the general system architecture for the realization of medical sensor networks including the model for hardware and software organization. Adherence to the general widely accepted system architecture should ensure the interoperability and interconnectivity among different medical systems based on wireless sensor networks (12, 13, 14). Finally, the paper analyzes the future development directions and possible benefits obtained by the implementation of the advanced medical systems based on sensor networks.

WIRELESS SENSOR NETWORKS

In the last decade, a new technology of wireless sensor networks (WSN) has emerged and become rapidly accepted and outspread worldwide. The most important prerequisites for the WSN development have been the advances in MEMS, wireless communications, microelectronics, embedded computing and sensing technology. These technological advances led to the development of the miniature multifunctional low-cost wireless sensor node which is equipped with data processing, storage, transceiver, power supply and sensing unit. The architecture of the typical sensor node is given in the Figure 1.

The data processing unit generally consists of the CPU (Central Processing Unit) and the associated storage unit. This unit coordinates all tasks related to the sensing and inter-node collaboration and communication. The transceiver unit enables mutual wireless communication between sensor nodes, such as the communication between nodes and base station. The battery is usually used as the power supply unit, although in some cases it can be extended with some energy scavenging unit (e.g. solar cells) or the power generator. The sensor node can also be extended with other optional application dependent units, such as the location finding system. The sensing unit usually consists of two main components: sensors and analog to digital converters (ADC).

The dispersed sensor nodes constitute the sensor field and form the multihop infrastructureless architecture. Each sensor node from the sensor field is capable of collecting data and routing them to the sink (base station). The data sink is connected to the end user or to the task manager node locally or remotely, via the Internet, GSM or other global network. The typical architecture of the sensor network is shown in Figure 2.

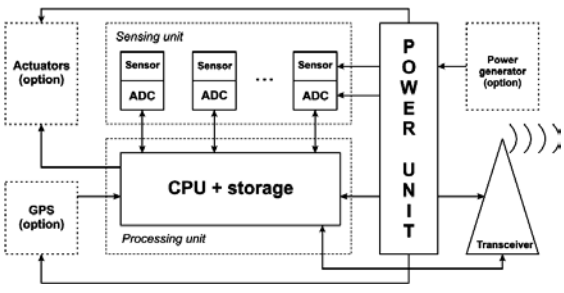


Figure 1. The architecture of the sensor node (Grgić K., 2011)

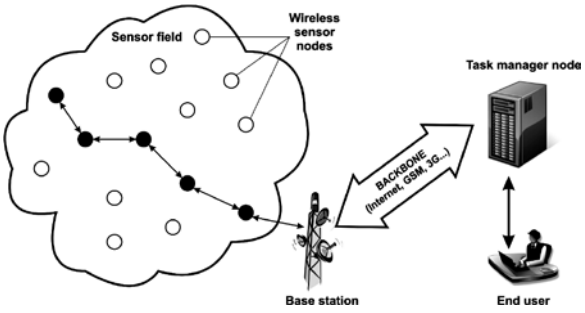


Figure 2. Typical architecture of the sensor network (Grgić K., 2011)

BODY AREA SENSOR NETWORKS

Application possibilities of wireless sensor networks are enormous. The WSNs are used worldwide for environmental applications (e.g. wildlife monitoring, fire and flood detection), military applications (battlefield surveillance, monitoring of forces and equipment), industrial and home applications, etc. Various applications led to the differentiation of wireless sensor networks to certain subclasses (e.g. vehicular sensor networks, environmental sensor networks). Recently, the BASN (Body Area Sensor Network) emerged as a specific subclass of the WSN, oriented towards the human body and its close surrounding (15, 16, 17, 18).

Body area sensor networks enable different novel and innovative applications in healthcare, fitness and entertainment. Similarly to the conventional WSN, the BASN also consists of multiple interconnected nodes capable of sensing, data processing and wireless communication. Specific for the BASNs is the fact that each sensor node is placed on, near or within the human body. In spite of high similarity with conventional WSNs, the BASNs set some strong challenges and requirements that have to be satisfied in order to achieve widespread adoption of such networks (19).

The BASN nodes have to be extremely non-invasive and therefore smaller than conventional WSN nodes. They also have to satisfy the requirements of safety and security (20, 21, 22, 23). Wearable and implantable sensors must be unobtrusive and bio-compatible, in order to prevent harm to the user (24). Privacy has to be ensured by using data encryption mechanisms for protection of potentially sensitive information. The ease of use and friendly user interface with intuitive controls should also be ensured.

The BASN node can be equipped with different types of sensors for monitoring the patient's physiological state (25). Depending on their specific purpose, these sensors can have many different forms – from standalone devices to the implants (26). The BASN sensor nodes constantly monitor different physiological signals, record them and perform their analysis (permanently or periodically). Some most frequently used sensors are sensors for monitoring the electrical activities of the heart (ECG), muscles (EMG) and the brain (EEG) (27, 28). The sensing nodes may also include temperature sensors (thermistors) for body temperature monitoring, glucose level sensors for blood glucose monitoring, blood pressure sensors, respiration sensors and sensors for monitoring of blood oxygen saturation (PPG) (29). The sensor set also often includes the additional non-physiological sensors. These additional sensors usually monitor the conditions of the patient's closer environment (e.g. ambient temperature, humidity, background light, atmospheric pressure) or the patient's exact position (GPS) (30, 31, 32). The BASN often includes the 3D accelerometer which serves for monitoring the patient's activity over a certain period and also enables the detection of falls (33, 34).

PROPOSED GENERAL TELEMEDICINE ARCHITECTURE

The general architecture of telemedicine system includes three main areas: local sensory area, communication network area, institutional network area.

The local sensory area consists of wireless body-area sensor networks attached to patients. Every patient has different medical sensors attached (e.g. ECG, blood pressure sensor, temperature sensor). Medical sensors support wireless communication, usually according to the ZigBee standard (due to its small energy consumption). Every patient is equipped with a small handheld device which acts as the body aggregator node. This device collects and aggregates the data obtained from medical sensors. It also serves as the direct interface to the patient. The handheld device provides locally obtained data directly to the patient, but also serves as the communication device for direct contact with the medical institution. The local aggregator node collects and aggregates data from multiple handheld devices

(from different patients) and forwards them to the communication network area.

Communication network area interconnects the local sensory area with the institutional network in a medical institution (e.g. hospital). Different types of networks can be used for this purpose, e.g. the Internet, cellular network (2G/3G), WiMAX. All obtained data are analysed, aggregated and stored into the database on the healthcare server. Every patient has his/her own record, properly secured and with restricted access. Medical personnel (e.g. physicians, nurses) have access to the patient records through the local secured institutional network. They may have different levels of access rights, according to the current institutional policies. The described architecture of the telemedicine system is illustrated in Figure 3.

A very important issue in telemedicine systems is to provide the security and privacy of patient-related data. Providing data security usually implies that the data is securely stored and transferred through the network. The data privacy connotes that the data can only be accessed by authorized personnel. Securely stored data means that their confidentiality and integrity are assured. The stored data should also be retrievable in case of failure of sensor node or handheld device.

Data access security implies the implementation of fine-grained data access policy that prevents the unauthorized access to sensitive patient-related data. The authentication of data sender should also be ensured in order to prevent the injection of false data from the outside. Constant availability of patient data is also an imperative.

Data security and privacy are usually ensured by implementation of different encryption schemes, usually based on predistributed shared keys. The implementation of security mechanisms represents a big challenge due to strong resource constraints of sensor nodes. Therefore, the security mechanisms need to be as lightweight as possible for a specific application.

It is also important to standardize the interfaces between different components of the telemedicine system. Such approach enables an easier expansion of the system, as well as an easier interconnection, integration and data exchange between different systems. At the same time, the interface for the patients has to be user friendly and easy to use.

BASN EXAMPLES WORLDWIDE

Body area sensor networks represent the fundamental basis for the mobile healthcare systems (often denoted as the mHealth systems). Such systems are currently the subject of intensive research efforts worldwide (35, 36, 37). These efforts have resulted in certain mHealth systems which are already in practical use, but are also under further development (38, 39, 40). There are also several mHealth systems that are in a development phase under some active research project (41). The individual body area sensor networks are usually interconnected with other modern communication networks (the Internet, cellular networks) forming a complex global system (42). The interconnection of BASN networks with the Internet or cellular network enables remote patient monitoring through the telemedicine system (43, 44). This article gives a short survey of some existing mHealth and telemedicine systems, which may be useful for the medical practitioners and researchers, but also for the engineers interested in the area of sensor networking. Mobile

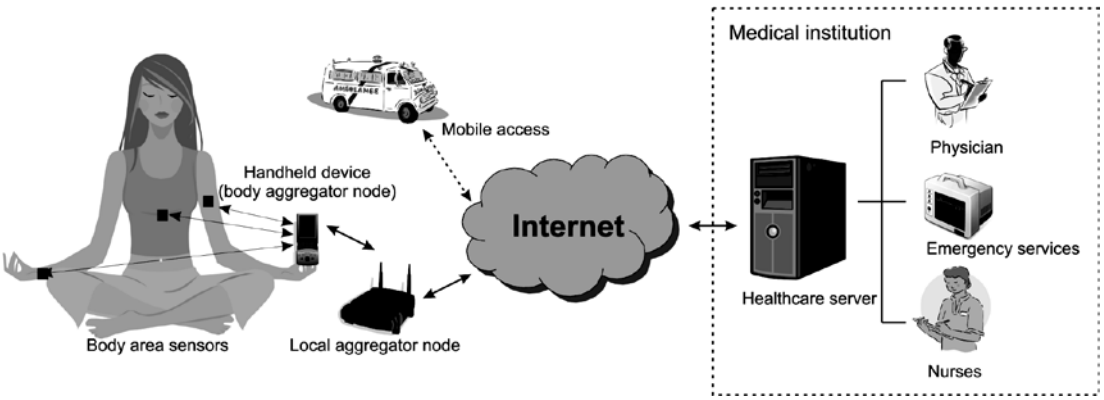


Figure 3. General architecture of the telemedicine system (Grgić K., 2011)

healthcare and telemedicine systems represent the intensively developing area, and thus it is impossible to cover all existing systems in a single article (45, 46, 47). Therefore, some examples are chosen in order to represent the possibilities and further development directions of such systems.

CodeBlue

The Harvard University developed the CodeBlue telemedicine system that quickly became one of the most popular worldwide (48, 49). CodeBlue represents an ad hoc sensor network infrastructure intended for the emergency medical care. The system is based on tiny sensor nodes for monitoring of patients' vital parameters – pulse, ECG and oximetry. Sensor nodes forward the collected data to the fixed terminal devices or mobile handheld devices wirelessly. The set of available sensors is constantly extending, since many companies develop different types of wireless vital sign sensors. The obtained medical data can be displayed in real-time or stored into database for each individual patient. The alarm is automatically triggered if some observed vital parameters deviate from regular values. Besides the hardware infrastructure, a fully scalable software platform intended for wireless medical devices was developed. CodeBlue software platform performs networking functions (route discovery and routing, traffic classification), provides database interface and management functions, and implements adequate security mechanisms (for encryption and authentication). CodeBlue system also includes the positioning and location tracking subsystem, for monitoring exact locations of patients (indoor and outdoor).

AMON

Project sponsored by the EU IST (European Union Information Society Technologies) resulted in the development of AMON device (Advanced care and alert portable telemedical MONitor) (50). It is primarily intended for continuous medical monitoring of high-risk cardiac/respiratory patients. AMON is a wrist-worn device that enables continuous collection and evaluation of multiple vital signs, including pulse, blood pressure and oxygenation, ECG, heart rhythm and skin temperature. The device can also be extended with additional medical sensors (e.g. glucose sensor). AMON also integrates the acceleration sensor intended to detect the level of the user activity and to correlate it with obtained vital parameters. The wrist-worn AMON device performs the online analysis of all obtained sensor measurements, presents the analysis results to the patient, and also sends them to the remote telemedicine centre via cellular network (GSM or UMTS). Through the analysis of vital signs the AMON device detects the emergency conditions and triggers the alarm in the telemedicine centre. The AMON device has a very flexible communication interface that enables the use of both direct connection and SMS services, and provides a direct contact between the medical personnel and the patient in emergency situations. The main disadvantage of the AMON system is the fact that most measurements obtained from sensors cannot be directly used for clinical purposes because they are not precise enough (e.g. a precise ECG cannot be obtained from a wrist device).

IBM Personal Care Connect

The IBM Company also entered the area of telemedicine systems through the development of a standardized platform called Personal Care Connect (PCC), intended for remote patient monitoring and providing interfaces for various biomedical sensor devices (51). The platform consists of a data collecting component that performs sensing and forwarding of the obtained measurements to the server. The server processes the data, stores it into a database, and presents the data in an adequate form on the interface. The PCC platform is an open and extendable platform, so sensor devices from different vendors can be easily integrated. The platform also provides the application programming interfaces (API) which enable the application vendors to implement their software solutions independently on the device technologies that have been used. Such approach significantly reduces costs and the time of the development of the telemedicine system. The core of the system is a Java-based module with interfaces for the communication with medical devices that support Bluetooth wireless communication standard. The advanced cell phone or personal digital assistant supporting Java and Bluetooth can be used as a data aggregator.

Smart Medical Home

The University of Rochester developed the concept of the Smart Medical Home, located within the University's Center for Future Health (52).

The Smart Medical Home actually represents the controlled environment available for an interdisciplinary research. The main project goal was the development of the Personal Health System which seamlessly integrates different technologies allowing personal medical care for patients in the privacy of their own homes. The Smart Medical Home is equipped with different monitoring devices, including video cameras and infrared sensors (for motion detection and patient tracking), biomedical sensors (for measurements of vital signs – pulse, blood pressure, respiration) and computers. The obtained data is continuously provided to physicians and medical institutions. The concept of the Smart Medical Home leads to the future development of a virtual personal medical advisor which could actively interact with the patient.

AlarmNet

The University of Virginia introduced the ALARM-NET (Assisted-Living and Residential Monitoring Network) prototype of the wireless sensor network intended for the assisted-living and residential monitoring (53). Its heterogeneous architecture integrates environmental and physiological sensors and enables continuous patient monitoring. The sensor set includes infrared, temperature, light, pulse and blood oxygenation sensors. The system also implements the CAR analysis program (Circadian Activity Rhythm) that analyses the rhythmic behavioural activities of patients in order to detect any behavioural changes within the behavioural patterns, because these changes may indicate certain health problems. Advanced algorithms for security, data privacy and power management are also implemented.

Secure Mobile Computing

Another project at the University of Virginia called the Secure Mobile Computing using Biotelemetrics also led to the development of the remote medical monitoring system (54). The sensing device is patch-shaped and includes the biometric sensor (ECG), the microcontroller and the Bluetooth radio. The device is battery-powered, but there are research efforts aiming to achieve the operation by harvesting energy from the human body (e.g. from the body temperature or motion). The sensing device is connected via Bluetooth link to the PDA device, which performs data logging and analysis. The PDA device is programmed to detect any anomalies in biometric signals according to its pre-programmed policies. The system implements the service-oriented architecture in order to achieve a high interoperability with other systems and to leave possibilities for further expansions.

Medical MoteCare

The Medical MoteCare is the prototype of the health monitoring system developed by the Sydney University of Technology (55). The core of the system is wireless sensor network based on MicaZ sensor nodes (by Crossbow). The sensing nodes are equipped with pulse oxymeter sensors and environmental sensors (temperature and light). The main parts of the system are the sensor nodes (motes), the Stargate personal server with data acquisition board (by Crossbow), the monitor unit and the network management server. The sensor nodes collect the relevant patient data and send them wirelessly (by using ZigBee – IEEE802.15.4 communication standard) to the Stargate personal server. The Stargate personal server supports IEEE802.11 (Wi-Fi), GSM and GPRS communication standards for the interconnection with other devices. A personal server connects to monitoring unit, which captures the obtained data and store it locally on log files. With an adequate software support the monitor unit acts as a data delivery unit which transmits the collected data into the TCP/IP based network. The network management server analyzes the obtained medical data and manages possible critical situations when the observed parameters deviate from their standard values.

MEMS Wear

The MEMSWear represents the biomonitoring system for the remote monitoring of vital signs, developed by the National University of Singapore (56). This system integrates wireless body area network and personal digital assistant (PDA) technology. The platform includes two different sensors: ECG sensor and integrated SpO2/temperature sensor. Such platform provides monitoring of four different physiological signs: ECG, SpO2, body temperature and blood pressure. Sensors are incorporated into a wearable shirt platform, in

order to be non-invasive for the patient. The obtained physiological data is transferred via Bluetooth communication standard to the patient's PDA. The Patient's data is further relayed to the doctor's PDA via GSM cellular network.

MEDIC

The MEDIC (Medical Embedded Device for Individualized Care) represents an open and extensible architecture which can be used in patient monitoring applications and medical diagnoses, with a support for remote configuration and control by medical professionals (57). It was developed at the University of California, Los Angeles (UCLA). Numerous physiological sensors are located on various body parts and they communicate with a wearable computer. The system may also include different contextual sensors located in a patient's closer environment. The wearable computer hosts a diagnostic engine which processes the local data and detects patient's condition. As a wearable computer the PDA or a cell phone are normally used. The wearable computer presents the information to the patient through the graphical user interface (GUI), and at the same time it communicates with remote servers located in medical institutions allowing medical personnel to view the obtained data and perform the diagnostic process. In case of emergency, the doctor is able to obtain a direct real-time control of the diagnostic processes.

In conclusion, the technology of wireless sensor network has recently experienced a significant development. It has become widely accepted and it is used in many applications worldwide. Its further evolution has led to the development of body area sensor networks (BASN), as its special subdivision. The BASN networks are oriented towards the human body and its closer surrounding. The wireless nodes of the BASN network equipped with different types of physiological sensors provide a possibility of constant monitoring of the patient's vital functions and a quick reaction in case of emergency.

The BASN networks represent the basis for building complex telemedicine systems for remote patient monitoring. Such non-invasive systems improve the quality of the patient's life and enable constant monitoring of his physiological parameters, as well as a prompt reaction in emergency cases.

The article gives a short overview of some telemedicine systems based on the BASN networks in order to illustrate the current state and emphasize the directions for the future development of such systems. The article also proposes a general architecture for telemedicine systems, which should be modular with standardized interfaces among different modules.

Some problems regarding the patient-related data security and privacy are also emphasized. Quality solutions for these problems will increase the confidence for telemedicine systems and contribute to their further development as well as wider acceptance and use.

This article should introduce the reader with telemedicine systems and the BASN networks as their core part. The short overview of the existing systems, that are used worldwide, should increase the interest for telemedicine and the BASN networks and raise confidence for such systems, among both - patients and medical personnel. This technology has a great potential for the further development and a wide implementation with a direct and significant influence on the quality of life.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Yick Y, Mukherjee B, Ghosal D. Wireless sensor network survey. Computer Networks 2008; 52:2292-330.
2. Akyildiz IF, Su W, Sankarasubramaniam Y, Cayirci E. Wireless sensor networks: a survey. Computer Networks 2002; 38:393-422.
3. Chan M, Esteve D, Escriba C, Campo E. A review of smart homes – present state and future challenges. Comput Methods Programs Biomed 2008; 91:55-81.
4. Lin CC, Lee RG, Hsiao CC. A pervasive health monitoring service system based on ubiquitous network technology. Int J Med Inf 2008; 77:461-9.
5. ZigBee Alliance. ZigBee Wireless sensor applications for health, wellnes and fitness. [Online] http://www.zigbee.org/imwp/download.asp?ContentID=15585 (15 September 2010)
6. Kyriacou E, Voskarides S, Pattichis CS, Istepanian R, Pattichis MS, Schizas CN. Wireless telemedicine systems: a brief overview. [Online] http://www.ivpcl.org/N2.pdf (15 March 2010)

7. Pattichis CS, Kyriacou E, Voskarides S, Pattichis MS, Istepanian R, Schizas CN. Wireless telemedicine systems: an overview. IEEE Antenna's and Propagation Magazine 2002; 2:143-53.
8. Lee YD, Chung WY. Wireless sensor network based wearable smart shirt for ubiquitous health and activity monitoring. Sensors and Actuators B 2009; 140:390-5.
9. Garcia-Saez G, Hernando ME, Martinez-Sarriegui I, Rigla M, Torralba V, Brugues E, De Leiva A, Gomez EJ. Architecture of a wireless Personal Assistant for telemedical diabetes care. Int J Med Inf 2009; 78:391-403.
10. Shin DI, Shin KH, Kim IK, Park KS, Lee TS, Kim SI, Lim KS, Huh SJ. Low-power hybrid wireless network for monitoring infant incubators. Med Eng Phys 2005; 27:713-6.
11. Demongeot J, Virone G, Duchene F, Benchetrit G, Herve T, Noury N, Rialle V. Multi-sensors acquisition, data fusion, knowledge mining and alarm triggering in health smart homes for elderly people. C R Biol 2002; 325:673-82.
12. Varshney U. A framework for supporting emergency messages in wireless patient monitoring. Decision Support Systems 2008; 45:981-96.
13. Golmie N, Cypher D, Rebala O. Performance analysis of low rate wireless technologies for medical applications. Computer Communications 2005; 28:1266-75.
14. Parera AJ, Angulo BC, Cabestany CJ. ZigBee Communication when building a body sensor network for elderly people. Proceedings of the 6th International Conference of the International Society for Gerontechnology, Pisa, Italy, 4-7 June 2008. [Online] http://www.gerontechnology.info/Journal/Proceedings/ISG08/papers/063.pdf (15 August 2010)
15. Hanson MA, Powell HC, Barth AT, Ringgenberg K, Calhoun BH, Aylor JH, Lach J. Body area sensor networks: challenges and opportunities. IEEE Computer 2009; 1:58-65.
16. Lo BPL, Thiemjarus S, King R, Yang GZ. Body sensor network – a wireless sensor platform for pervasive healthcare monitoring. [Online] http://www.pervasive.ifi.lmu.de/adjunct-proceedings/demo/p077-080.pdf (14 August 2010)
17. Brady S, Carson B, O'Gorman D, Moyna N, Diamond D. Body sensor network based on soft polymer sensors and wireless communications. Journal of Communications 2007; 5:1-6.
18. Yang GZ. Body sensor networks. London: Springer, 2006.
19. Lorincz K, Malan DJ, Fulford-Jones TRF, Nawoj A, Clavel A, Shnayder V, Mainland G, Welsh M. Sensor networks for emergency response: challenges and opportunities. IEEE Pervasive Computing 2004; 4:16-23.
20. Li M, Lou W, Ren K. Data security and privacy in wireless body area networks. IEEE Wireless Communications 2010; 1:51-8.
21. Malasri K, Wang L. Design and implementation of a secure wireless mote-based medical sensor network. Proceedings of the 10th International Conference on Ubiquitous Computing, Seoul, Korea, 21-24 September, 2008. [Online] http://netlab.cs.memphis.edu/papers/ubicomp08.pdf (1 June 2010)
22. Misic J, Misic VB. Implementation of security policy for clinical information systems over wireless sensor networks. Ad Hoc Networks 2007; 5:134-44.
23. Malasri K, Wang L. Securing wireless implantable devices for healthcare: ideas and challenges. IEEE Communications Magazine 2009; 7:74-80.
24. Almudevar A, Leibovici A, Tentler A. Home monitoring using wearable radio frequency transmitters. Artif Intell Med 2008; 42:109-20.
25. Engin M, Demirel A, Engin EZ, Fedakar M. Recent developments and trends in biomedical sensors. Measurement 2005; 37:173-88.
26. Valdastri P, Rossi S, Menciassi A, Lionetti V, Bernini F, Recchia FA, Dario P. An implantable ZigBee ready telemetric platform for in vivo monitoring of physiological parameters. Sensors and Actuators A 2008; 142:369-78.
27. Gyselinckx B, Penders J, Vullers R. Potential and challenges of body area networks for cardiac monitoring. J Electrocardiol 2007; 40:165-68.
28. Lai CC, Lee RG, Hsiao CC, Liu HS, Chen CC. A H-QoS-demand personalized home physiological monitoring system over a wireless multi-hop relay network for mobile home healthcare applications. Journal of Network and Computer Applications 2009; 6:1229-41.
29. Chang WY, Fang TH, Lin YC. Characterization and fabrication of wireless flexible physiological monitor sensor. Sensors and Actuators A 2008; 143:196-203.
30. Benini L, Farella E, Guiducci C. Wireless sensor networks: Enabling technology for ambient intelligence. Microelectronics Journal 2006; 37:1639-49.
31. Jones VM, Mei H, Broens T, Widya I, Peuscher J. Context aware body area networks for telemedicine. Proceedings of the 8th Pacific Rim Conference on Advances in Multimedia Information Processing, Hong Kong, China, 11-14 December 2007. [Online] http://eprints.eemcs.utwente.nl/11640/01/1569055303.pdf (1 June 2010).
32. Lee HJ, Lee SH, Ha KS, Jang HC, Chung WY, Kim JY, Chang YS, Yoo DH. Ubiquitous healthcare service using Zigbee and mobile phone for elderly patients. Int J Med Inform 2009; 78:193-8.
33. Sneha S, Varshney U. Enabling ubiquitous patient monitoring: model, decision protocols, opportunities and challenges. Decision Support Systems 2009; 46:606-19.
34. Bang M, Timpka T. Ubiquitous computing to support co-located clinical teams: using the semiotics of physical objects in system design. Int J Med Inform 2007; 765:558-64.
35. Virone G, Wood A, Selavo L, Cao Q, Fang L, Doan T, He Z, Stoleru R, Lin S, Stankovic JA. An advanced wireless sensor network for health monitoring. [Online] http://www.cs.virginia.edu/papers/d2h206-health.pdf (1 June 2010)
36. Dokovsky N, Van Halteren A, Widya I. BANip: enabling remote healthcare monitoring with body area networks. FIDJI 2003 International Workshop on Scientific Engineering of Distributed Java Applications, Luxembourg-Kirchberg, Luxembourg, 27-28 November, 2003. Abstract LNCS 2952, p. 62-72. Springer-Verlag, Berlin, Germany.
37. Maglogiannis I, Hadjiefthymiades S. EmerLoc: Location-based services for emergency medical incidents. Int J Med Inform 2007; 76:747-59.
38. Krco S. Health care sensor networks – architecture and protocols. Ad Hoc & Sensor Wireless Networks 2005; 1:1-25.
39. Koch S. Home telehealth – current state and future trends. Int J Med Inform 2006; 75:565-76.

40. Jurik AD, Weaver AC. Remote medical monitoring. IEEE Computer 2008; 4:96-9.
41. Van Halteren A, Bults R, Wac K, Dokovsky N, Koprinkov G, Widya I, Konstantas D, Jones V. Wireless body area networks for healthcare: the MobiHealth project. In: Lymberis A, De Rossi D, eds. Wearable eHealth Systems for Personalised Health Management, Studies in Health Technology and Informatics. Netherlands: IOS Press, 2004; 181-93.
42. Aquino-Santos R, Potes AG, Rangel-Licea V, Garcia-Ruiz MA, Villasenor-Gonzalez LA, Edwards-Block A. Wireless communication protocol based on EDF for wireless body sensor networks. Journal of Applied Research and Technology 2008; 2:120-30.
43. Stankovic JA, Cao Q, Doan T, Fang L, He Z, Kiran R, Lin S, Son S, Stoleru R, Wood A. Wireless sensor networks for in-home healthcare: potentials and challenges. [Online] http://smart-attire.cs.uiuc.edu/files/hcmdss-05.pdf (1 June 2009)
44. Milenkovic A, Otto C, Jovanov E. Wireless sensor networks for personal health monitoring: issues and an implementation. Computer Communications 2006; 29:2521-33.
45. Feng DD. Biomedical information technology. London: Academic Press, 2008.
46. Xiao Y, Chen H. Mobile telemedicine – a computing and networking perspective. Boca Raton: CRC Press, 2008.
47. Yang L, Hussain S, Laforest F, Verdier C. Pervasive health care services and technologies. International Journal of Telemedicine and Applications 2008. [Online] http://downloads.hindawi.com/journals/specialissues/0332008001.pdf (15 July 2010)
48. Malan D, Fulford-Jones T, Welsh M, Moulton S. CodeBlue: an ad hoc sensor network infrastructure for emergency medical care. Proceedings of Workshop on Applications of Mobile Embedded Systems, Boston, USA, 6 June 2004. [Online] http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.62.5465 (1 July 2010)
49. Shnayder V, Chen BR, Lorincz K, Fulford-Jones TRF, Welsh M. Sensor networks for medical care. Proceedings of the 3rd international conference on embedded networked sensor systems, San Diego, USA, 2-4 November 2005. [Online] http://portal.acm.org/citation.cfm?id=1098979 (1 July 2010)
50. Anliker U, Ward JA, Lukowicz P, Troster G, Dolveck F, Baer M, Keita F, Schenker E, Catarsi F, Coluccini L, Belardinelli A, Shklarski D, Alon M, Hirt E, Schmid R, Vuskovic M. AMON: a wearable multiparameter medical monitoring and alert system. IEEE Trans Inf Technol Biomed 2004; 4:415-27.
51. Blount M, Batra VM, Capella AN, Ebling MR, Jerome WF, Martin SM, Nidd M, Niemi MR, Wright SP. Remote health-care monitoring using Personal Care Connect. IBM Systems Journal 2007; 1:95-114.
52. Center for Future Health. http://www.futurehealth.rochester.edu/smart_home/ (1 June 2010)
53. Wood A, Virone G, Doan T, Cao Q, Selavo L, Wu Y, Fang L, He Z, Lin S, Stankovic J. ALARM-NET: wireless sensor networks for assisted-living and residential monitoring. Technical Report CS-2006-13. University of Virginia (Department of Computer Science), 2006. [Online] http://www.cs.virginia.edu/wsn/medical/pubs/tr06-alarmnet.pdf (15 June 2010)
54. Hu J, Weaver AC. A dynamic, context-aware security infrastructure for distributed healthcare applications. [Online] http://www.cs.virginia.edu/~acw/security/doc/Publications/A%20Dynamic,%20Context-Aware%20Security%20Infrastructure%20for%20Distri~1.pdf (15 June 2010)
55. Navarro KF, Lawrence E, Lim B. Medical MoteCare: a distributed personal healthcare monitoring system. Proceedings of International Conference on eHealth, Telemedicine, and Social Medicine, Cancun, Mexico, 1-7 February 2009. [Online] http://www.computer.org/portal/web/csdl/doi/10.1109/eTELEMED.2009.19 (1 June 2010)
56. Tay FEH, Guo DG, Xu L, Nyan MN, Yap KL. MEMSWear – biomonitoring system for remote vital signs monitoring. Journal of the Franklin Institute 2009; 6:531-42.
57. Wu WH, Bui AAT, Batalin MA, Au LK, Binney JD, Kaiser WJ. MEDIC: medical embedded device for individualized care. Artif Intell Med 2008; 42:137-52.

Medicinske primjene bežičnih senzorskih mreža – trenutno stanje i buduće smjernice

Krešimir Grgić, Drago Žagar, Višnja Križanović

Zavod za komunikacije, Elektrotehnički fakultet, Sveučilište "J. J. Strossmayer", Osijek, Hrvatska

SAŽETAK

Proteklih godina zabilježen je značajan razvoj tjelesnih senzorskih mreža kao posebne podvrste bežičnih senzorskih mreža. Ove mreže omogućile su ubrzani razvoj telemedicinskih sustava koji omogućavaju udaljeni nadzor pacijenata i njihovih vitalnih parametara. U radu se daje kratki pregled tjelesnih senzorskih mreža, te je predložena opća arhitektura telemedicinskih sustava. Predložena arhitektura uključuje lokalno senzorsko područje, područje komunikacijske mreže i područje mreže unutar medicinske institucije. Ona također omogućava sigurnost i privatnost podataka o pacijentima. Nadalje, članak daje pregled nekih postojećih telemedicinskih sustava, ističe neke postojeće probleme, te daje smjernice budućeg razvoja.

Ključne riječi: bežične mreže, senzori, telemedicina

ORIGINAL ARTICLE

Influence of short-term changes in sex hormones on serum concentrations of cellular adhesion molecules in young healthy women

Ivana Begić[1], Ana Čavka[2], Martina Mihalj[2], Tatjana Baćun[1], Ines Drenjančević[2]

[1] Internal Medicine Clinic, University Hospital Centre of Osijek, Osijek, [2]Department of Physiology and Immunology, School of Medicine of the University "Josip Juraj Strossmayer"; Osijek, Croatia

ABSTRACT

Aim To determine if short-term changes in sex hormones (such as cyclic changes within the menstrual cycle) can influence the serum concentration of soluble cell adhesion molecules (CAMs).

Methods Sixteen healthy young women with normal cycles participated in this study. Serum levels of sICAM-1, sVCAM-1 and E-selectin were determined in three different phases of the menstrual cycle: a) early follicular (EF) phase, b) ovulatory (O) phase and c) midluteal (ML) phase, by standardized ELISA-based kits. To confirm the exact assessment of menstrual cycle phases, serum levels of estrogen, progesterone, LH and FSH were measured.

Results There were significant oscillations in serum female sex hormones concentration over the cycle duration, as expected the level of estrogen (E2) and progesterone (PROG) was the lowest in EF phase, the highest E2 appeared in O phase, and both E2 and PROG were present in high concentrations during ML phase. There was a significant positive correlation between E2 and serum soluble ICAM -1 concentrations (p=0,041, correlation coefficient 0,306). However, there was no significant change in other soluble CAMs concentration during the menstrual cycle.

Conclusion Results of our study suggest that short-term changes in female sex hormone levels could modulate expression of soluble ICAM-1, but not VCAM -1 or E-selectin in extent that would affect a young woman's health.

Key words: cell adhesion molecules, female sex hormones, sICAM-1, sVCAM-1, E-selectin

Corresponding author:
Ines Drenjančević
Department of Physiology and Immunology, School of Medicine University Josip Juraj Strossmayer; Osijek
Josipa Huttlera 4, 31000 Osijek, Croatia
Phone: +385 31 512 882;
fax: +385 31 512 866;
E-mail: ines.drenjancevic@mefos.hr

Original submission:
28 June 2011;
Revised submission:
20 August 2011;
Accepted:
21 August 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):32-36

INTRODUCTION

Estrogens and especially 17β-estradiol (E2) are hormones known to play a key role in female sexual development and reproduction, but recently estrogenic role in various physiological processes of different organ systems, including cardiovascular system have also been described (1). Cardiovascular diseases are more common in postmenopausal than premenopausal women, suggesting protective vascular effect of E2. Previous studies revealed that E2 protects against atherosclerosis which has been explained by direct effects of E2 on vascular wall (2-5). It has been indicated that E2 affects vascular function by modulating vasodilator and vasoconstrictor systems (6,7). It has been shown that E2 also promotes vascular healing by remodelling vascular wall while inhibiting smooth muscle cell proliferation and accelerating reendothelialization of injured blood vessels (8). Furthermore, it prevents activation of endothelium as well as the vascular inflammatory response by inhibiting cytokine production, cytokine-induced expression of cell adhesion molecules and platelet aggregation/adhesion.

Cellular adhesion molecules (CAMs) are cell surface molecules crucial for cell trafficking throughout the organism. Soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and E-selectin are endothelium derived CAMs. It has been shown that various factors can affect the level of CAMs expression (i.e. high lipid intake, weight, menopause) thus changing the inflammatory status of a woman and her susceptibility to development of cardiovascular disease (9). Accordingly, soluble CAMs measured in plasma may serve as useful markers for vascular inflammation and thrombus formation (10). Previous studies have reported an increase of CAMs in postmenopausal women, when the female sex hormones decline, while the hormonal replacement therapy was successful in decreasing levels of soluble CAMs. Piercy et al. demonstrated that combined estrogen and progesterone exposure significantly decreased the expression of VCAM-1 and ICAM-1 in cell cultures of normal human female iliac artery stimulated endothelial cells (11). Koh et al. reported improvement in endothelium-dependent vasodilator responsiveness and effects on markers of inflammation, hemostasis, and fibrinolysis inhibition in healthy postmenopausal women subjected to estrogen and progesterome exposure (12).

Even though a large number of studies have shown positive impact of female sex hormone restoration on vascular function and decreased expression of soluble CAMs in postmenopausal women, data on the impact of female sex hormone fluctuations during the normal menstrual cycle on endothelial function and expression of soluble CAMs are insufficient.

The aim of this study was to determine if the short-term changes in sex hormones (such as cyclic changes within the menstrual cycle) can influence the serum concentration of soluble CAMs.

PATIENTS AND METHODS

Ethical approval

All participants gave their written informed consent and did not receive any compensation for taking part in this study. Study conformed to the standards set by the latest revision of the *Declaration of Helsinki* and was approved by the Ethical Committee of the School of Medicine, Osijek, Croatia. This study was performed in collaboration with the Clinical Hospital Center of Osijek, Croatia.

Participants

Sixteen healthy young women (M 23±0,25 year; range 22-24), all students at the School of Medicine Josip Juraj Strossmayer University of Osijek (Croatia), volunteered to participate in this study. A short survey was carried out among second to fourth year medical students to select only those young women who (a) had had regular menstrual cycles (i.e. 28 ± 2) with no history of skipping cycles and (b) had not been using oral contraceptives (OC) six months prior to engagement in this study. They were subjected to tests at three different phases of the menstrual cycle: (a) from 2nd to 4th day of the menstrual cycle in early follicular phase, (b) in proven ovulatory phase, and (c) 7th to 9th days later in mid-lutheal phase. Urinary strips were used to determine the date of ovulation ELISA-based LH. Hormone levels in the assigned phases of the menstrual cycle were assessed from venous blood to confirm menstrual cycle phases.

Hormone levels

Serum levels of E2, PROG, LH, follicle stimulating hormone (FSH) and testosterone (TESTO) were assessed from venous blood. The blood was taken and immediately delivered to the Department of Nuclear Medicine and Radiation Protection at the University Hospital Centre of Osijek, where hormone levels were determined as a part of routine diagnostic procedure by using standard radioimmunoassay (RIA) kits (BioSource Europe S.A., Belgium).

Before the results of hormone levels measured from venous blood were available, commercial ELISA-based LH urinary stripes (Biostrip LH Ovulation Test, Innovatek Medical inc., Vancouver, B.C., Canada) were used to determine preovulatory increase of LH.

Detection of soluble CAMs

Serum levels of sICAM-1, sVCAM-1 and E-selectin were measured. After taking blood, serum was collected and stored at -80ºC. Serum levels of soluble CAMs were assessed by using commercially available ELISA based kits (Quantikine Immunoassay ELISA human sICAM-1/CD54, sE-Selectin/CD62E, sVCAM-1, R&D Systems, UK). Final concentrations were determined by using standardized concentration curves.

Statistics

All data values are presented as means ± SEM and analyzed by One-Way ANOVA repeated measures or Freedman's test followed by post hoc Tukey and Holm-Sidac tests when appropriate (SigmaPlot 11.,0). The correlation between CAMs and hormones was determined by Persons' coefficient or Sperman's test. Level of statistical significance was determined at $p<0.05$.

RESULTS

Hormone levels

The results of the hormones' serum concentrations showed that the participants underwent blood withdrawal for CAMs determination at appropriate points of the menstrual cycle. All measured hormone levels were among referent values set by the routine diagnostic laboratory where the blood was analyzed.

Table 1. Hormone levels during the menstrual cycle

Hormone	EF phase	O phase	ML phase	P*
E2 (pmol/ml)	207.50±14,52	877.06±96.08	615.19±72.76	<0.001
LH (IU/L)	3.41±0,36	16.56±4.76	3.10±0.40	<0.001
FSH (IU/L)	6.25±0,50	7.01±1.06	2.91±0.25	<0.001
PROG (nmol/ml)	4.98±0,36	15.80±3.72	51.24±6.44	<0.001
TESTO (pmol/ml)	1.48±0,15	2.28±0.17	2.06±0.22	<0.002

Table 2. CAMs levels among the menstrual cycle phases

Hormone	EF phase	O phase	ML phase	P
ICAM-1 (ng/ml)	298.59±44.83	342.96±38.68	320.54±39.14	0.781
VCAM-1 (ng/ml)	516.89±43.22	534.43±34.11	525.63±31.10	0.778
E-selectin (ng/ml)	24.84±2.82	23.64±2.22	23.76±2.14	0.923

* Results are presented as mean ± SEM, and are not statistically significant

Table 1 shows the mean level of E2, PROG, LH, FSH and TESTO at the time when the participants were subjected to the test sessions. LH and E2 were the highest in O phase which, together with a positive result on the ovulation detection kit showed that all presented participants had ovulatory cycles and were tested on time. The E2 level during ML phase was at least twice as high as in EF phase ($p<0,001$) which fulfills the criteria established by Hollander et al. (2005). The E2 level in O phase was higher than in ML phase in all tested women but there was no statistically significant difference. The highest PROG level was in ML phase of the cycle ($p<0,001$). All participants had TESTO concentration among referent values during entire menstrual cycle (referral values: 0,38-2,74 nmol/L).

Serum CAMs' levels

Serum levels of sICAM-1, sVCAM-1 and E-selectin did not vary significantly among the menstrual cycle phases (Table 2). However, E2 and ICAM-1 showed a tendency to increase together ($p=0,041$, correlation coefficient 0,306) (Figure 1.). No other significant correlation between CAMs and measured hormones (PROG, LH, FSH and TEST) could be found.

DISCUSSION

Numerous studies conducted in postmenopausal woman have shown positive effect of estrogen

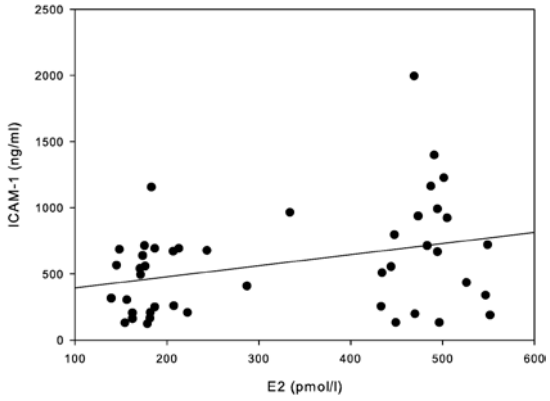


Figure 1. Correlation between E2 and ICAM-1*
*statistically significant (p=0,041) and showed a tendency of E2 and ICAM-1 to increase together

replacement therapy on endothelial function, assessed by measuring serum levels of CAMs as indirect markers of endothelial dysfunction (3-5). These studies demonstrated reduced CAMs expression after exposure to estrogen, implicating lower susceptibility to inflammatory processes in vessels' walls. On the contrary, only a few studies have investigated effects of short-term variations in female sex hormones on CAMs expression, such as menstrual cycle variations in estrogen and progesteron levels (11, 12). Souter and al. have demonstrated that long-term exposure to exogenous estrogens suppresses serum levels of sVCAM-1, but short-term changes in endogenous estrogens, as during the menstrual cycle, may not alter VCAM-1 expression (13). On the other hand, four years later, the same author has shown that gonadotropin-induced changes in E2 (in vitro fertilization cycle) significantly alter serum levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) (14). On the other hand, study by Elhadd et al investigating levels of CAMs in three different phases of the menstrual cycle in young healthy normal cycling women reported that changes in estrogen levels during the menstrual cycle can significantly alter the levels of E-selectin, but not ICAM-1 (15). However, studies relying only on counting of the cycle days backwards from the predicted first day of next menstrual cycle to determine cycle phases are questionable. Therefore, in our study, menstrual cycle phases were assessed by measuring hormone levels in blood and additionally, LH levels by LH urinary strips in urine.

Although the experimental methodology was significantly improved in our study, there was a significant positive correlation between E2 and serum soluble ICAM -1 concentrations (Figure 1). However, we were not able to detect any significant change in other soluble CAM concentrations during the menstrual cycle. These results suggest that short-term changes in sex hormone levels could modulate expression of ICAM-1, but not VCAM -1 or E-selectin to the extent that would affect a young woman's health.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Arnal JF, Fontaine C, Billon-Galés A, Favre J, Laurell H, Lenfant F, Gourdy P. Estrogen receptors and endothelium. Arterioscler Thromb Vasc Biol 2010; 30:1506-12.
2. Gourdy P, Mallat Z, Castano C, Garmy-Susini B, Mac Gregor JL, Tedgui A, Arnal JF, Bayard F. The atheroprotective effect of 17 beta-estradiol is not altered in P-selectin- or ICAM-1-deficient hypercholesterolemic mice. Atherosclerosis 2003; 166:41-8.
3. Khalil RA. Potential approaches to enhance the effects of estrogen on senescent blood vessels and postmenopausal cardiovascular disease. Cardiovasc Hematol Agents Med Chem 2010; 8:29-46.
4. Joswig M, Hach-Wunderle V, Ziegler R, Nawroth P. Postmenopausal hormone replacement therapy and the vascular wall: Mechanisms of 17 β-estradio's effects on vascular biology. Exp Clin Endocrinol Diabetes 1999; 107:477-87.
5. Brzezinski A, Danenberg HD. Estrogen, progesterone, and cardiovascular health: when shall we complete the puzzle? Menopause 2005; 12:488-91.
6. Duckles SP, Miller VM. Hormonal modulation of endothelial NO production. Pflugers Arch 2010; 459:841-51.
7. Chakrabarti S, Lekontseva O, Peters A, Davidge ST. 17beta-Estradiol induces protein S-nitrosylation in the endothelium. Cardiovasc Res 2010; 85:796-805.
8. Filipe C, Shang Leen LL, Brouchet L, Billon A, Benouaich V, Fontaine V, Gourdy P, Lenfant F, Arnal JF, Gadeau AP, Laurell H. Estradiol accelerates endothelial healing through the retrograde commitment of uninjured endothelium. AJP 2008; 94: H2822-H2830.
9. Toth B, Nikolajek K, Rank A, Nieuwland R, Lohse P, Pihusch V, Friese K, Thaler CJ. Gender-specific and menstrual cycle dependent differences in circulating microparticles. Platelets 2007; 18:515-21.

10. Raitakari OT, Celermajer DS. Testing for endothelial dysfunction. Ann Med 2000; 32: 293-304.
11. Piercy KT, Donnell RL, Kirkpatrick SS, Timaran CH, Stevens SL, Freeman MB, Goldman MH. Effects of estrogen, progesterone, and combination exposure on interleukin-1 beta-induced expression of VCAM-1, ICAM-1, PECAM, and E-selectin by human female iliac artery endothelial cells. J Surg Res 2002; 105:215-9.
12. Koh KK, Jin DK, Yang SH, Lee SK, Hwang HY, Kang MH, Kim W, Kim DS, Choi IS, Shin EK. Vascular effects of synthetic or natural progestagen combined with conjugated equine estrogen in healthy postmenopausal women. Circulation 2001; 103:1961-6.
13. Souter I, Janzen C, Martinez-Maza O, Breen EC, Stanczyk F, Chaudhuri G, Nathan L. Serum levels of soluble vascular cell adhesion molecule-1 are decreased in women receiving oral contraceptives compared with normally menstruating women: implications in atherosclerosis. Fertil Steril 2005; 83:1480-8.
14. Souter I, Huang A, Martinez-Maza O, Breen EC, Decherney AH, Chaudhuri G, Nathan L. Serum levels of soluble vascular cell adhesion molecule-1, tumor necrosis factor-alpha, and interleukin-6 in in vitro fertilization cycles. Fertil Steril 2009; 91(Suppl 5): 2012-9.
15. Elhadd TA, Neary R, Abdu TA, Kennedy G, Hill A, McLaren M, Akber M, Belch JJ, Clayton RN. Influence of the hormonal changes during the normal menstrual cycle in healthy young women on soluble adhesion molecules, plasma homocysteine, free radical markers and lipoprotein fractions. Int Angiol 2003; 22:222-8.

Utjecaj kratkotrajnih promjena spolnih hormona na serumske koncentracije staničnih adhezivnih molekula mladih zdravih žena

Ivana Begić[1], Ana Čavka[2], Martina Mihalj[2], Tatjana Baćun[1], Ines Drenjančević[2]

[1]Klinika za internu medicinu, Klinički bolnički centar Osijek, [2]Medicinski fakultet Sveučilišta ž'Josipa Juraja Strossmayera''; Osijek, Hrvatska

SAŽETAK

Cilj Odrediti utjecaj kratkotrajnih promjena koncentracije spolnih hormona (kao što su cikličke promjene za vrijeme menstruacijskog ciklusa) na serumsku koncentraciju topljivih staničnih adhezivnih molekula (engl. *CAMs*).

Metode Šesnaest zdravih mladih žena, s normalnim ciklusima, sudjelovalo je u ovoj studiji. Serumske koncentracije sICAM-1, sVCAM-1 i E-selektina izmjerene su u tri različite faze menstruacijskog ciklusa: a) ranoj folikularnoj fazi (EF), b) ovulatornoj fazi (O) i c) midlutealnoj fazi (ML); pomoću standardnih ELISA kitova. Serumske koncentracije estrogena, progesterone, LH I FSH mjerene su kako bi se potvrdila točnost određivanja faze menstruacijskog ciklusa.

Rezultati Izmjerene su značajne oscilacije koncentracije ženskih spolnih hormona u serumu, tijekom trajanja ciklusa; kao što je i očekivano, koncentracija estrogena (E2) i progesterona (PROG) bila je najniža u EF fazi; najviši E2 bio je u O fazi, a oba, E2 i PROG bila su izmjerena u visokoj koncentraciji u ML fazi. Postojala je značajna pozitivna korelacija između E2 i serumske topljive ICAM-1 (p=0,041, koeficijent korelacije 0,306). Međutim, nije bilo bilo kakvih značajnih promjena drugih CAMs koncentracija tijekom menstruacijskog ciklusa.

Zaključak Rezultati naše studije upućuju da kratkotrajne promjene koncentracije ženskih spolnih hormona mogu modulirati izražajnost topljive ICAM-1 molekule, ali ne i VCAM-1 ili E-selektina u tolikoj mjeri da bi utjecali na zdravlje mlade žene.

Ključne riječi: stanične adhezivne molekule, ženski spolni hormoni, sICAM-1, sVCAM-1, E-selektin

ORIGINAL ARTICLE

The effect of intravenous vitamin C on the phosphorus level reduction in hemodialysis patients: A double blind randomized clinical trial

Afshin Gholipour Baradari[1], Amir Emami Zeydi[2], Fatemeh Espahbodi[3], Mohsen Aarabi[4]

[1]Department of Anesthesiology and Intensive Care Medicine, School of Medicine, [2]Department of critical care nursing, School of Nursing and Midwifery, [3]Department of Nephrology, School of Medicine; Mazandaran University of Medical Sciences, Sari, [4]Department of Epidemiology, Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Iran

ABSTRACT

Aim The majority of hemodialysis patients are hyperphosphatemic. Hyperphosphatemia in these patients can lead to renal osteodystrophy, vascular calcification, cardiovascular events, and is independently associated with mortality risk. The aim of this study was to evaluate the effect of intravenous vitamin C on phosphorus level in hemodialysis patients.

Methods Using a double blind randomized clinical trial, a total of 60 qualified hemodialysis patients were randomly allocated in two intervention and control groups and serum phosphorus, CRP, calcium, albumin and PTH levels were measured. At the end of each hemodialysis session, intervention group received vitamin C vial (500mg/5cc) intravenously three times a week for 8 weeks and control group received normal saline in the same way. Data were collected before and after two months of treatment. Data were analyzed using independent t-test, paired t-test and chi-square test.

Results Vitamin C treated group had a significant decrease in phosphorus (p=0.01), CRP level (p=0.01) and Ca×P product (p=0.03). In contrast, there was no significant difference in phosphorous (p= 0.5) and CRP levels (p= 0.6) and Ca×P product (p=0.7) in the control group. In addition, there was no statistically significant change in calcium (p=0.1), PTH (p=0.4) and albumin (p=0.4) levels in both groups.

Conclusion Intravenous vitamin C can significantly decrease phosphorus level in hemodialysis patients.

Key words: hemodialysis, phosphorus, vitamin C, hyperphosphatemia, Ca×P product, CRP

Corresponding author:
Amir Emami Zeydi
Department of Medical Surgical Nursing,
Nasibeh Nursing and Midwifery Faculty
Vesal Street, Amir Mazandarani Boulevard, Sari/ Iran, PO BOX: 481675793
Phone/Fax: +98 1512267342-5
E-mail: research9090@yahoo.com

Original submission:
26 September 2011;
Revised submission:
08 November 2011;
Accepted:
30 Neovember 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):37-41

INTRODUCTION

Hyperphosphatemia is a common complication in patients with end stage renal disease (ESRD) undergoing hemodialysis. Untreated hyperphosphatemia might lead to renal osteodystrophy, vascular calcification, and cardiovascular events causing increased morbidity and mortality (1). Studies suggest that serum phosphate greater than 6.5 mg/dL is associated with 27% higher mortality risk compared to patients with phosphate level of 2.4–6.5 mg/dL (2). Hence, phosphorus control in patients on hemodialysis constitutes one of the most important issues that nephrologists are faced with today. Successful control of phosphorus is one of the key aspects in the management of hemodialysis patients (3). However; phosphate control has not been significantly improved over the past two decades (2). Also association between change in calcium, phosphorous and their product (Ca×P product) and increased cardiovascular mortality and morbidity in ESRD patients undergoing chronic dialysis has been described (4). Maintenance hemodialysis patients are especially predisposed to vitamin C deficiency because of dietary restrictions, malnutrition and clearance of vitamin C during dialysis treatment and this deficiency may have an important impact on patient outcomes (5). One single hemodialysis session may result in a 50 to75% decrease in plasma vitamin C level, which predicts adverse cardiovascular outcomes in maintenance hemodialysis patients (6). Therefore, to reach normal levels of vitamin C, it is necessary to prescribe vitamin C supplements to all hemodialysis patients (5).

Considering the fact that vitamin C can reduce the CRP level and CRP reduction directly correlates with phosphorus reduction (7, 8), we hypothesized that vitamin C can decrease phosphorus level in hemodialysis patients. The purpose of this study was to evaluate the effect of intravenous vitamin C on phosphorus level in hemodialysis patients.

PATIENTS AND METHODS

This study was a randomized double blind placebo-controlled clinical trial to evaluate the effect of intravenous vitamin C on phosphorus level in hemodialysis patients. A total of 60 hemodialysis patients in Imam Khomeini Hospital, Sari, Iran, were included in the study from 5/22/2010 to 8/19/2010. Patients with the age range of 20-70 years and serum phosphorus level above 5.5 mg/dl that had been hemodialysed three times a week on 4 hour sessions for at least 6 months prior to the trial, were enrolled in the study. Exclusion criteria were history of malignancy, malnutrition, severe cardiac or respiratory or liver disease, history of vitamin C, vitamin D, alcohol, oil fish and immunosuppressive drugs consumption during 2 months prior to the trial. Patients who refused to continue the study at any time or got systemic disease during the study were also excluded from the study. A list of random number generated by the random-number table was employed to allocate eligible patients into intervention and control groups. Intervention group received vitamin C vial (500mg/5cc) intravenously from the venous line at the end of each hemodialysis session three times a week for a period of 8 weeks and control group received 5cc normal saline as placebo in the same way. Neither patients nor clinicians were aware of the allocated group.

At the beginning of the study and before the last hemodialysis session, 10cc fasting venous blood samples were taken from the patients in order to measure serum phosphorus (P), calcium (Ca), CRP and parathyroid hormone (PTH) levels. Patients were asked not to change their nutrition, drugs and physical activity during the study. Phosphorus level was measured using Pars Azmoon Company Kit and photometric technique by BT3000 and serum total calcium was measured with ortho-cresolphthalein complexone (o-CPC) and then the Ca×P product was calculated. Serum CRP was measured with Norway Kit (England) and Nephelometric method and PTH level by radio immunoassay technique and Gamma Counter. Moreover, all patients in the two groups received calcium-based phosphate binder (calcium carbonate) and those who received aluminum hydroxide were excluded from the study. In both groups patients were dialyzed by Fresenius 4008B Hemodialysis Machine and single use polysulfone membrane. Dialysate calcium concentration was 1.2 mmol /L and all patients had arteriovenous (AV) fistula.

Data were collected and analyzed using SPSS version 16 and chi-square test, Fisher exact test, independent and paired t-test.

Approval from the Mazandaran University of Medical Sciences Ethics Committee and informed

written consent from patients were obtained. This study was registered in a clinical trials database (IRCT138904224365N1; http://www.irct.ir).

RESULTS

Sixty eligible hemodialysis patients were recruited in the period 5/22/2010 - 8/19/2010 and randomized into two groups. Two patients withdrew from the study (one patient in placebo group died and one patient in vitamin C group refused to continue the study) (Figure 1). Complete data were obtained from 58 hemodialysis patients with a mean age of 59.7 (14.6) years for the vitamin C group and 60.6 (13.3) years for the controls, which showed no significant difference between the two groups (p=0.7). The mean duration of hemodialysis in intervention and control group was 29±16.0 and 30.1±22.1 months, respectively, with no statistical significant differences between the two groups (p=0.8).

As shown in Table 1, there was no statistically significant difference in demographic and baseline characteristics of the patients between the two study groups.

Table 1. Demographics and clinical characteristic in intervention and control groups

Variables		No (%) of patients in group		p
		Vitamin C (n=29)	Placebo (n=29)	
Gender	Male	17 (58.6)	14 (48.3)	0.46
	Female	12 (41.4)	15 (51.7)	
Marital Status	Single	2 (6.9)	3 (10.3)	0.58
	Married	27 (93.1)	26 (89.7)	
Smoking	Yes	5 (17.2)	2 (6.9)	0.23
	No	24 (82.8)	27 (93.1)	
Cause of renal failure	Diabetes	6 (20.7)	11 (37.9)	0.34
	Hypertension	13 (44.8)	11 (37.9)	
	Other Causes	10 (34.5)	7 (24.1)	

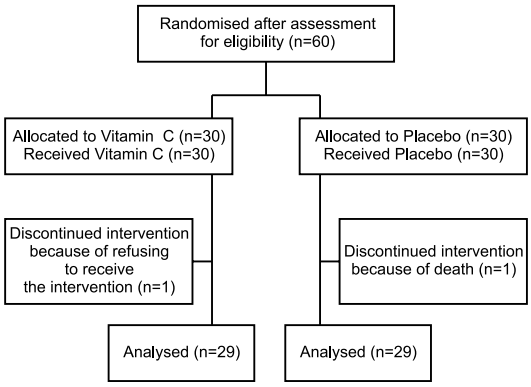


Figure 1. Flow diagram of the progress through the phases of trial of two groups

There was no significant differences in phosphorus (p=0.8), CRP (p=0.8), calcium (p=0.6) and PTH (p= 0.3) levels among the groups at the baseline. As shown in Table 2, compared to their baseline level, vitamin C treated group showed a significant decrease in phosphorus (p=0.013) and CRP levels (p=0.042), and Ca×P product (p=0.033) (Figure 2, Figure 3). In contrast, there were no significant differences in these parameters in the placebo group. Furthermore, mean differences (after – before) of phosphorus, CRP and Ca×P product were statistically significant

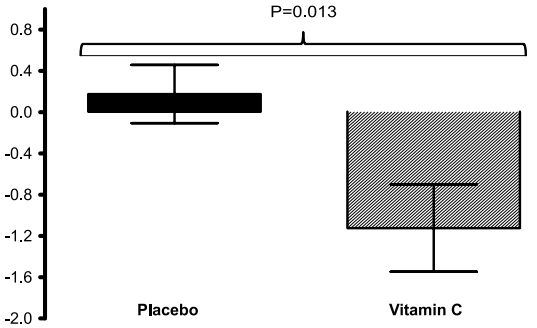


Figure 2. Phosphorous differences (after - before) in both groups (mean and SEM)

Table 2. Mean and standard deviation of phosphorus, Calcium, CRP, Albumin, PTH level and Ca x P product in hemodialysis patients before and after intervention in Vitamin C (n=29) and placebo (n=29) groups

Variable	Group	Before intervention Mean ± SD	After intervention Mean ± SD	p*	After - before Mean ± SD	p†
Phosphorus (mg/dl)	Placebo	6.02±2.37	6.2±2.02	0.5	0.18±1.53	0.013
	Vitamin C	6.11±2.1	4.98±1.97	0.01	-1.12±2.28	
Calcium (mg/dl)	Placebo	8.34±0.9	8.24±0.4	0.5	-0.9±0.84	0.226
	Vitamin C	8.24±0.75	8.42±0.56	0.2	0.18±0.86	
CRP (mg/dl)	Placebo	11.1±9.09	11.24±7.82	0.9	0.14±8.0	0.042
	Vitamin C	10.96±8.15	7.27±6.72	0.01	-3.7±7.7	
Albumin (mg/dl)	Placebo	4.42±0.5	4.34±0.4	0.5	-0.08±0.67	0.737
	Vitamin C	4.45±0.4	4.42±0.3	0.7	-0.03±0.57	
Ca×P product (Mg2×dl2)	Placebo	50.03±20.1	50.27±17.7	0.7	0.93±13.5	0.033
	Vitamin C	50.97±15.9	41.83±16.6	0.03	-8.4±20.2	
PTH (ng/l)	Placebo	198.5±120.3	194.6±115.4	0.3	-4.1±117.1	0.814
	Vitamin C	201.6±115.6	197.8±119.6	0.2	-3.9±116.5	

p*, paired t-test; p†, independent t-test

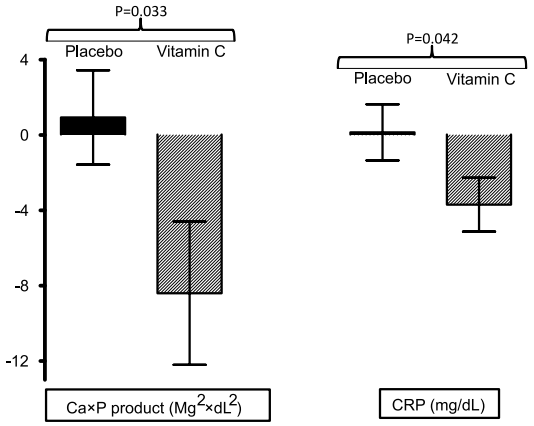


Figure 3. Ca x P product ($Mg^2 \times dl^2$) and CRP differences (after - before) in both groups (mean and SEM)

between the intervention and control groups. Changes in calcium, albumin and PTH levels were not different in both groups after the intervention (Table2).

DISCUSSION

The key and novel finding in the present study is a significant decrease in phosphorus level by eight week administration of intravenous vitamin C in hemodialysis patients. Considering the anti inflammatory and antioxidant effect of vitamin C (7) the paralleled reduction in phosphorus and CRP levels in the present study could be explained by some mechanisms which include: decrease in the cellular destruction and shift of phosphorus from the intra cellular to extra cellular fluid, recovery of cellular injury due to antioxidant effect and increased renal phosphate excretion, effect on metabolic acidosis and extracellular shift of phosphorus and effect on NaPi cotransporter and reducing phosphorus expression in proximal tubule (9). Adeney et al (10) suggested that higher serum phosphate concentration, although within the normal range, are associated with a greater prevalence of vascular and valvular calcification in people with moderate chronic kidney disease (CKD). Our study showed that vitamin C treated group, had a lower Ca×P product level after intervention. Ganesh et al (11) declared that for every 10 greater units of Ca×P product in hemodialysis patients, the relative risk of sudden death increased by 7%. Also, Mills et al (12) demonstrated that Ca×P product is associated with severity of aortic stenosis in hemodialysis patients. Chronic inflammation, as reflected by increased of inflammatory markers, such as CRP, is highly prevalent in hemodialysis patients (13) and increased level of CRP is a strong predictor of all-cause mortality, especially, the cardiovascular one in these patients (14). In this study, we found that the average concentration of CRP and phosphorus level was significantly lower in intervention group than in control group. Hung et al (15) observed a direct relationship between serum phosphorus and CRP in a cohort study. Moreover, Movilli et al (16) showed an association of the Ca×P product with the CRP levels. Block et al (7) have shown the CRP-lowering effect of vitamin C supplementation. Vitamin C represents anti-oxidant defense in blood and non-supplemented hemodialysis patients are at risk of vitamin C deficiency (6). Parenteral administration of ascorbic acid may be an approach to overcome problems of vitamin C deficiency in hemodialysis patients- in particular problems associated with iron overload, erythropoietin resistance and chronic inflammation (17). Fumeron et al (18) reported that oral administration of 250 mg/day of vitamin C after dialysis did not significantly change the oxidative stress and inflammation states, but the effect of high doses of intravenous administration was not clear. Parenteral vitamin C can improve erythropoiesis and decrease CRP level in hemodialysis patients (17). Major concern regarding safety of vitamin C supplementation is its metabolism to oxalate, which may develop to secondary oxalises (19) and one of the possible limitations of the present study was the lack of plasma oxalate level measurements. However, we used a dose of vitamin C that according to previous studies did not increase the plasma oxalate level after 8 weeks of treatment (17, 20). The statistical power of the study was calculated. The results indicated that assuming phosphorous mean difference of 1.30 (SD=1.75), a sample size of 29 in each group was adequate to provide 81% statistical power to compare study groups.

In conclusion, this study demonstrated that intravenous administration of vitamin C was effective in decreasing the phosphorus level in hemodialysis patients. The beneficial change made by intravenous vitamin C in phosphorus level introduces vitamin C as an attractive agent for future research and its use for patients who are on maintenance hemodialysis.

ACKNOWLEDGMENTS

The authors express their gratitude to the staff of Hemodialysis Center of Imam Khomeini Hospital (Sari, Iran) for their efficient and kind collaboration.

Also, the authors wish to thank all the study participants for their tremendous cooperation.

FUNDING

The financial support of Research Deputy of Mazandaran University of Medical Sciences is gratefully acknowledged.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Hutchison AJ, Speake M, Al-Baaj F. Reducing high phosphate levels in patients with chronic renal failure undergoing dialysis: a 4-week, dose-finding, open label study with lanthanum carbonate. Nephrol Dial Transplant 2004; 19:1902-6.
2. Mohammed IA, Hutchison AJ. Phosphate binding therapy in dialysis patients: focus on lanthanum carbonate. Ther Clin Risk Manag. 2008; 4:887–93.
3. Arenas MD, Malek T, Gil MT, Moledous A, Alvarez-Ude F, Reig-Ferrer A. Challenge of phosphorus control in hemodialysis patients: a problem of adherence?. J Nephrol 2010; 23: 525-34.
4. Egbuna OI, Taylor JG, Bushinsky DA, Zand MS. Elevated calcium phosphate product after renal transplantation is a risk factor for graft failure. Clin Transplant 2007; 21:558-66.
5. Richter A, Kuhlmann MK, Seibert E, Kotanko P, Levin NW, Handelman GJ. Vitamin C deficiency and secondary hyperparathyroidism in chronic haemodialysis patients. Nephrol. Dial Transplant 2008; 23:2058-63.
6. Deicher R, Ziai F, Bieglmayer C, Schillinger M, Horl WH. Low Total Vitamin C Plasma level is a risk factor for cardiovascular morbidity and mortality in hemodialysis patients. J Am Soc Nephrol 2005; 16:1811–8.
7. Block G, Jensen CD, Dalvi TB, Norkus EP, Hudes M, Crawford PB, Holland N, Fung EB, Schumacher L, Harmatz P. Vitamin C treatment reduces elevated C-reactive protein. Free Radic Biol Med. 2009; 46:70-7.
8. Calo LA, Savica V, Piccoli A, Fusaro M, Angelo AD, Davis PA. Reduction of hyperphosphatemia is related with the reduction of C- reactive protein in dialysis patients. Study in sevelamer-resistant dialysis patients treated with chitosan chewing gum as salivary phosphate binder. Renal Failure 2011; 33:11-4.
9. George AL, Neilson EG. Disorder of the kidney and urinary tract. In: Longo D, Fauci AS, Kasper D, Hauser S. Harrison's Principles of Internal Medicine. 18th ed. New York: McGraw-Hill, 2011.
10. Adeney KL, Siscovick DS, Ix JH, Seliger SL, Shlipak MG, Jenny NS, Kestenbaum BR. Association of serum phosphate with vascular and valvular calcification in moderate CKD. J Am Soc Nephrol 2009; 20:381-7.
11. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO (4), Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12:2131-8.
12. Mills WR, Einstadter D, Finkelhor RS. Relation of calciumphosphorus product to the severity of aortic stenosis in patients with normal renal function. Am J Cardiol 2004; 94:1196-8.
13. Stenvinkel P, Alvestrand A. Inflamation in end stage renal disease: sources, consequences, and therapy. Semin Dial 2002; 15:329-37.
14. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis 2000; 35:469-76.
15. Huang HY, AppelL J, ChoiM J, Gelber AC, Charlesto J, Norkus EP, Miller ER. The effects of vitamin C supplementation on serum concentrations of uric acid. Arthritis Rheumatism 2005; 52:1843-7.
16. Movilli E, Feliciani A, Cammerini C. A high calcium-phosphate product is associated with high C-reactive protein concentrations in hemodialysis patients. Nephron Clin Pract 2005; 101:c161-c167.
17. Biesalski HK. Parenteral ascorbic acid in haemodialysis patients. Curr Opin Clin Nutr Metab Care 2008; 11:741-6.
18. Fumeron C, Nguyen-khoa T, SaltielC,Kebede M, Buisson C, Drueke TB, Lacour B, Massy ZA. Effects of oral vitamin C supplementation on oxidative stress and inflammation status in haemodialysis patients. Nephrol Dial Transplant 2005; 20:1874-9.
19. Tarng DC. Novel aspects of vitamin C in Epoetin response. J Chin Med Assoc 2007; 70:357-60.
20. Espahbodi F, Kashi Z, Ala S, Hendoii N. Efficacy and safety of oral versus intravenous vitamin C in hemodialysis patients with functional iron deficiency. Int J Endocrinol Metab 2007; 3:129-34.

ORIGINAL ARTICLE

Aortic flow propagation velocity as an early predictor of high coronary risk in hypertensive patients

Mustafa Yıldırım[1], Omer Yiginer[2], Mehmet Uzun[2], Bekir Yilmaz Cingozbay[2], Cemal Sag[1], Hasan Kutsi Kabul[1], Omer Uz[2], Zafer Isilak[2], Ejder Kardesoglu[2], Bekir Sitki Cebeci[2]

[1]Department of Cardiology, Gulhane Military Medical School, Etlik, Ankara, [2]Department of Cardiology, Gulhane Military Medical Academy, Uskudar, Istanbul; Turkey

ABSTRACT

Aim To assess the value of aortic flow propagation velocity (Vp) in detecting hypertensive patients with coronary risk.

Methods The study included 120 patients with hypertension. According to the 10-year risk of coronary heart disease the patients were categorized in the three groups: 10-year risk <10% (I),10-year risk=%10-20 (II), and 10-year risk >20% (III). The aortic flow propagation velocity (Vp) was measured from descending aorta with color M-mode echoardiography. The slope of the first aliasing contour was accepted as Vp. It was compared with Framingham coronary risk score, carotid intima media thickness and high sensitive C-reactive protein. Twelve patients were excluded from the study due to poor acoustic window.

Results The Vp was significantly lower ($p<0.001$), carotid intima media thickness and high sensitive C-reactive protein was significantly higher in group III ($p=0.002$ and $p=0.014$). The area under ROC curve of Vp, carotid intima media thickness and high sensitive C-reactive protein were 0.890, 0,700 and 0.664, respectively. There was a significant inverse relation between Vp and carotid intima media thickness ($r=-0.37$; $p<0.001$).

Conclusion The aortic flow propagation velocity is a simple, feasible and reproducible marker of atherosoclerosis with an acceptable sensitivity and specificity. There is a need for longitudinal prospective studies to use it routinely.

Key words: atherosclerosis, flow propagation velocity, carotid intima media thickness, high sensitive C-reactive protein

Corresponding author:
Omer Yiginer
GATA Haydarpasa Egitim Hastanesi
Kardiyoloji servisi- Uskudar
34667, Istanbul; Turkey
Phone: + 90 50 581 85 590;
fax.: 90 21 654 22 000;
E-mail: oyiginer@yahoo.com

Original submission:
04 April 2011;
Revised submission:
15 June 2011;
Accepted:
18 June 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):42-48

INTRODUCTİON

Atherosclerosis and related complications are the leading cause of death (1). Its early diagnosis and treatment is very important for decreasing cardiovascular deaths. There has been substantial number of investigations in this area, especially in coronary atherosclerosis, in the last four decades (2-4). The major difficulty in diagnosis of coronary atherosclerosis is to detect those patients who are at high risk but without any symptoms (3). In the detection of such patients, some risk scoring systems are suggested. Framingham Coronary Risk Scoring (FCRS) is the mostly used one (5). In this scoring system, 10-year risk of future coronary event is graded according to the LDL- and HDL-cholesterol levels, gender, blood pressure, smoking, diabetes mellitus and age. However, in a study by Khot et al (6), it was found that 40% of those patients with coronary artery disease have only one traditional risk factor while a substantial amount of others does not have any. Therefore, there happened a shift from treatment according to the risk factors to treatment according to the early diagnosis of atherosclerosis.

There are some parameters that are frequently used for early diagnosis of atherosclerosis. A new parameter with higher diagnostic power, which is user friendly, and cheaper than the other methods would be helpful in assessment of atherosclerosis (3, 4). For this aim, we compared the aortic flow propagation velocity (Vp) with carotid intima media thickness (IMT), high sensitive C-reactive protein (hs-CRP) as markers of atherosclerosis and coronary risk in patients with essential hypertension.

PATIENTS AND METHODS

The patients

The study included 120 consecutive patients with hypertension who had been admitted to outpatient cardiology clinics of Gulhane Military Medical Academy during September 2005. The inclusion criteria were the presence of essential hypertension, age >18 years of age, and acceptance of participation in the study. The exclusion criteria were the presence of heart valve disease, pericardial effusion (effusion less than 5 mm adjacent to the posterior wall was accepted normal), previous aortic or heart surgery, any active infection, any malignancy, hematocrite <36% or >52%, pacemaker implantation, acute coronary syndrome in previous 6 months, impaired systolic function (left ventricular ejection fraction <40%), using antihypertensive treatment, declining to participate in the study.

Definitions

The definitions used in the study were hypertension (blood pressure >140/90 mmHg on three consecutive measurements with one week intervals, smoking (cigarette smoking for at least one year), diabetes mellitus (meeting the criteria proposed by the American Diabetes Association) (7), Framingham Coronary Risk Score (FCRS) (coronary risk score as defined in the related study) (8).

The patients were grouped according to the 10-year risk of coronary heart disease in the three groups: 10-year risk <10% (I), 10-year risk=%10-20 (II), and 10-year risk >20% (III).

Ultrasonographic examinations

All patients were asked to rest and not to smoke or eat or drink anything for at least one hour before echocardiographic examination. The ECG was used to adjust appropriate timing. The examinations were made with Vivid 3 echocardiography device (GE, Norway) equipped with 3 MHz transducer for cardiac examination and 7.5-10 MHz transducer for carotid examination. The cardiac examination was performed while the patient was in lateral decubitus position. The carotid examination was performed while the patient is in supine position and head slightly directed towards the opposite side of the examined artery. The aortic examination was performed while the patient is in supine position with all extremities extended in a relaxed tone. The routine cardiac examination included all M-mode, B-mode, Doppler and Color Doppler examinations (9).

The measurements

Aortic flow propagation velocity (Vp). During aortic examination, the transverse and descending aorta was viewed from suprasternal window. The ultrasonic beam was alligned parallel to the lumen of descending aorta with the cursor located at the center of the lumen.(Figure 1) The color M-mode recording of the proximal descending aorta was obtained. The aliasing velocity

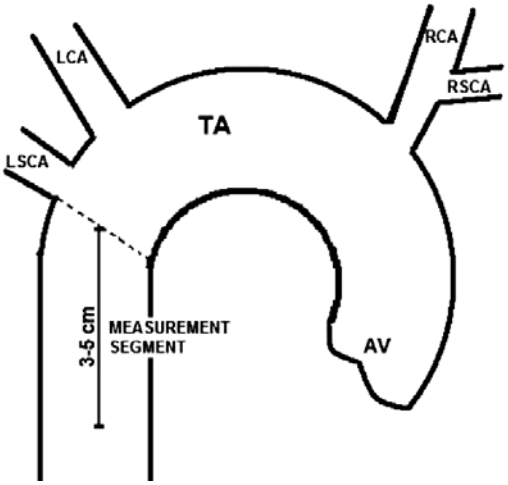


Figure 1. The illustration of measurement of aortic flow propagation velocty in descending aorta (AV, aortic valve; TA, transverse aorta; LSCA, left subclavian artery; LCA, left carotid artery; RCA, right carotid artery; RSCA, right subclavian artery) (Uzun M., 2005)

was adjusted to 40-50 cm/sec. On this recording, the slope of the first aliasing contour was measured. (Figure 2A and 2B). The average of 8-10 consecutive measurements was accepted as Vp.

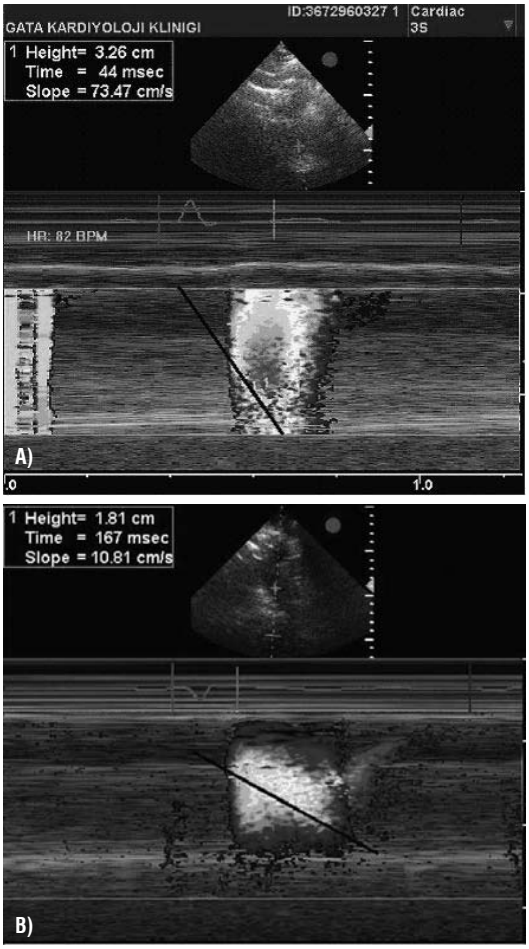


Figure 2. (A) Aortic flow propagation velocity in a normal patient, (B) Aortic flow propagation of a patient with high risk (Uzun M., 2005)

The peak velocity of blood at the proximal descending aorta was measured at the same view and location with pulsed wave Doppler.

The carotid IMT. Firstly, the common carotid artery was found in transverse section. Afterwards, the carotid artery was viewed in longitudinal section. The probe was displaced cranially until the internal carotid artery is viewed in its maximum diameter. The IMT was defined as the distance between the first echogenic line (lumen-intimal intersection) and second echogenic line (media-adventitia intersection). All measurements were performed in enddiastole (peak of R wave in ECG). In each patient, the IMT was measured six times from distal part of the lumen in two segments: common carotid and internal carotid artery. The maximum value was used in the analysis. All views were recorded in digital media in order to provide a second investigator blind to the other findings to perform the same measurements.

Statistical analysis

For statistical analysis, the SPSS version 13.0 in Windows (Chicago, USA) was used. The continuous variables were expressed as mean±1 standard deviation. The comparison among more than two groups was made by nonparametric Kruskal-Wallis test. The comparison between two groups was made by Mann-Whitney U test. The comparison between two parameters were made by linear regression analysis. The significance of p value was set at 0.05.

RESULTS

Twelve patients were excluded from the analysis due to poor acoustic window, therefore the statistical analysis included 108 patients (90%) (52 female; age=52±9 years). The comparison of categorical variables is shown in Table 1 and continuous variables in Table 2. Among the categorical variables, the coronary artery disease and diabetes mellitus was significantly higher

Table 1. The comparison of categorical variables

Parameter	Group I	Group II	Group III	p
Male gender	13	10	29	0.414
Smoking	5	8	13	0.074
Diabetes mellitus	2	0	12	0.038
Family history	4	0	10	0.074
Coronary artery disease	0	0	18	0.000

Table 2. Comparison of continuous variables*

Parameters	Group I	Group II	Group III	p value
Age	49±8	49±8	54±8	0,003
Left IMT	7,3±1,3	7,0±1,0	9,0±3,2	0,002
Right IMT	7,3±1,3	7,0±1,3	8,9±3,6	0,030
Waist/hip ratio	0,90±0,08	0,94±0,08	0,94±0,08	0,146
Body mass index	29±4	30±4	28±3	0,606
Microalbuminuria	9,0±8,3	7,6±6,2	8,9±15,9	0,815
Fibrinogen	333±49	373±58	352±66	0,099
hs-CRP	2,3±2,7	3,6±4,0	4,0±2,9	0,014
Sedimentation	12±7	17±13	13±9	0,617
Üre	27±6	30±8	30±8	0,135
Kreatinin	0,9±0,1	0,9±0,1	1,0±0,8	0,439
Ürik asit	4,8±1,7	5,0±1,7	5,3±1,3	0,446
LDL-cholesterol	118±31	138±31	126±32	0,031
VLDL-cholesterol	26±12	33±16	39±24	0,016
HDL-cholesterol	55±11	53±4	49±9	0,017
LVIDd	47±4	48±3	48±4	0,542
IVSd	12±2	11±2	12±3	0,143
PWd	10±2	11±1	11±2	0,379
LA	34±3	34±4	38±4	0,000
Ao	27±4	30±3	28±4	0,054
Aort peak velocity	97±16	93±12	91±16	0,324
Vp	58±10	54±8	37±13	0,000

*IMT, intima media thickness; hs-CRP, high sensitive CRP; LDL, low density lipoprotein; VLDL, very low density lipoprotein; HDL, high density lipoprotein; LVIDd, left ventricular diastolic internal dimater; IVSd, diastolic interventricular septal thickness; PWd, diastolic posterior wall thickness; LA, left atrium; Ao, aortic diameter; Vp, propagation velocity.

and smoking and family history were borderline higher in group III. There was no difference between groups I and II.

Among the continuous variables, age, left IMT, right IMT, high sensitive C-reactive protein, VLDL-cholesterol and left atrial diameter was higher and HDL-cholesterol was lower in group III. LDL-cholesterol was lower in group III in comparison with group II.

Table 3. The value of markers for predicting high risk patients for atherosclerosis estimated by ROC values

Parameter	Area under curve	Cut-off	Sensitivity (%)	Specificity (%)	p
Vp (cm/s)	0,890	≤46,5	84	85	0.000
Maximum IMT (mm)	0,673	≥0,8	66	73	0.003
Left IMT (mm)	0,700	≥0,7	64	68	0.000
Right IMT (mm)	0,643	≥0,7	61	59	0.013
hs-CRP (IU)	0,664	≥2,7	73	67	0.005

Vp, aortic flow propagation velocity; IMT, intima media thickness; hs-CRP, high sensitive C-reactive protein.

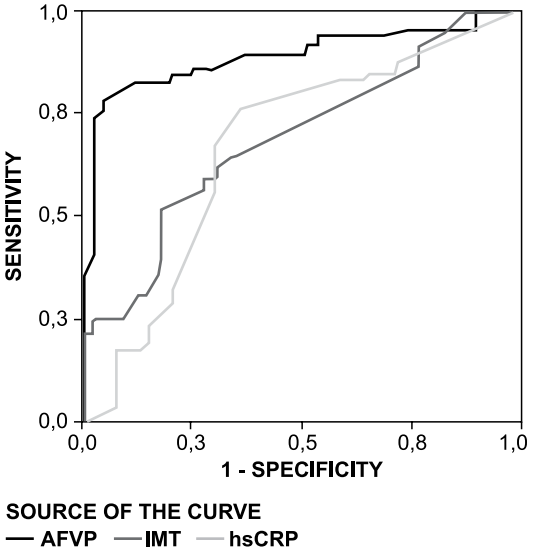


Figure 3. ROC curves of aortic flow propagation velocity, carotid intima media thickness and high sensitive C-reactive protein for predicting 10 year risk ≥ 20% (area under ROC curves are 0.890, 0.700 and 0.664, respectively)

The ROC curve of aortic flow propagation velocity for predicting high risk patients (Group III) is shown in Figure 3. The area under ROC curves for other markers of atherosclerosis that reached statistical significance, their best cut-off values, sensitivity and specificity corresponding to this cut-off value is shown in Table 3. The area under ROC curves of microalbuminuria and fibrinogen were not statistically significant. The addition of the aortic peak velocity (peak velocity/Vp) did not improve the predictive power of Vp significantly.

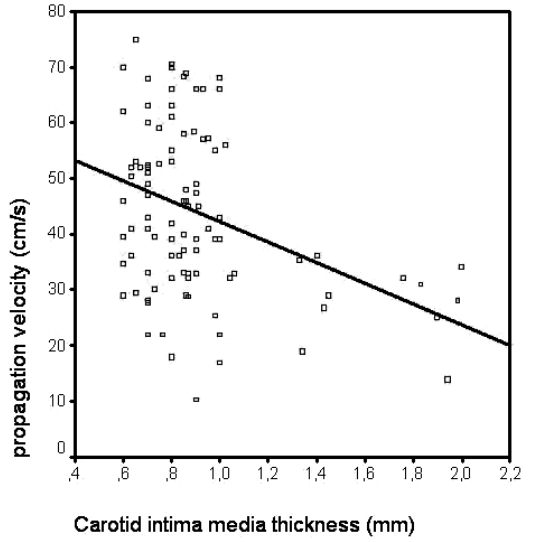


Figure 4. Lineer regression analysis of aortic flow propagation velocity and carotid intima media thickness

There was a significant inverse relation between Vp and carotid IMT (Figure 4; r=-0.37; p<0.001). However, the relation between Vp and hs-CRP was borderline (r=-0.18; p=0.077), while there was no relation between microalbuminuria and Vp (p=0.620).

The interobserver variability of the Vp was 4% and intraobserver variability was 3%.

DISCUSSION

Early noninvasive diagnosis of coronary atherosclerosis was made possible with the introduction of electron beam computed tomography (10) and magnetic resonance coronary angiography (11). However, these methods are expensive for routine use. Based on the fact that atherosclerosis is a systemic disease of vessels, changes in other arteries were also investigated as a surrogate marker of coronary atherosclerosis (3). This approach assumes that presence of an atherosclerotic disease in any region of the vascular system is suggestive for high risk for coronary atherosclerosis (2-4).

Among the noninvasive markers of atherosclerosis, flow-mediated dilatation of brachial artery and carotid IMT are the mostly used examples (2). Because the measurement of flow-mediated dilatation is a time-consuming process, its use is limited to investigations of endothelial functions (2,3). The IMT is widely used for assessment of atherosclerosis but there are some limitations for its use, such as wide range of normals, difficulty in imaging the carotid artery, variability in place of measurement (12). Therefore, a new, user friendly parameter for predicting coronary risk would be helpful (2-5).

The results of this study have shown that Vp is a promising, simple and feasible parameter for predicting high coronary risk patients. According to the results of this study, there were two reasons for this conclusion. Firstly, Vp was significantly related to Framingham Risk Score, and secondly, it was also significantly related to carotid IMT and hsCRP, which are accepted to be useful markers for atherosclerosis. These relations enabled us to discriminate high coronary risk patients with a good sensitivity and specificity. The carotid IMT was also discriminative but had a less predictive power.

We could not find other investigations about the aortic flow propagation, however, there are many studies about the mitral flow propagation (13). The application of same principles to the descending aorta has created the idea of Vp. It was shown that the mitral flow propagation velocity is highly dependant on the left ventricular diastolic function (13-15). The relaxation of the left ventricle decreases the resistance to flow coming through mitral valve (13). If the relaxation process happens more quickly and completely, the propagation of coming flow occurs more rapidly. The left ventricular relaxation could be influenced by many factors, including remodeling and ischemia as the most frequent ones (13, 14). When the same principles are applied to the descending aorta, the left atrium substitutes with transvers aorta and left ventricle substitutes with distal arterial bed (13,14). Accordingly, the relaxing function of left ventricle is represented by the expanding capacity of the distal arterial bed, namely the elasticity of the arteries. If the distal arterial tree expands more rapidly, the propagation velocity is expected to be more rapid and vice versa. The elasticity of the distal arterial tree is also dependant on many factors but remodeling is the most frequent one (16). The ischemia takes little part in functions of arterial bed (16).

A significant relation between hsCRP and Vp was found in this study. The hsCRP has established as a marker of generalized atherosclerosis in many studies (17). In our study, it was also related to a coronary risk. The Vp was also in inverse relation with the hsCRP, suggesting that Vp may also be a sign of atherosclerosis. The relation between carotid IMT and atherosclerosis has also been well documented (18,19). In our study, there was an inverse relation between carotid IMT and atherosclerosis.

In the present study, there were no relations between microalbuminura and Vp was established although it was shown that the microalbuminuria could be a marker for atherosclerosis (20). The absence of the relation may be explained by the fact that micoalbuminuria was abnormally high in only one patient. In this patient, the Vp was low (36 cm/s), too. Another explanation might be that the Vp was related to large arteries while microalbuminuria is associated with damage in small arteries.

One limitation of the study was an inclusion of only hypertensive patients. The validity of the AFVP was previously shown in a whole popula-

tion by Uzun et al (21). Therefore, this study was designed to assess its validity in a different population, in which the atherosclerosis is an important concern. Moreover, aortic distentibility was not evaluated. If it was evaluated, establishing a pathopyhsiological casual relationship would be more precise. On the other hand, Gullu et al (22) have shown that there was a significant relation between noninvasive predictors of atherosclerosis, including carotid intima-media thickness and aortic stiffness. The relation between carotid IMT and Vp might indirectly suggest a relation between aortic stiffness and Vp.

In conclusion, the aortic flow propagation velocity is a simple, feasible and reproducible marker of atherosoclerosis with an acceptable sensitivity and specificity. However, the evidence presented in this study was based on indirect measures of atherosclerosis. There is a need for longitudinal prospective studies to use it routinely.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. World Health Organization. The world health report 1999 making a difference. Geneva: WHO, 1999.
2. Bolad I, Delafontaine P. Endothelial dysfunction: its role in hypertensive coronary disease. Curr Opin in Cardiol 2005; 20:270-4.
3. Mark DB, Shaw LJ, Lauer MS, O'Malley PG, Heidenreich P. Task force 5 Is atherosclerosis imaging cost effective? J Am Coll Cardiol 2003; 41:1906-17.
4. Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL Jr, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Russell RO, Smith SC JrAmerican College of Cardiology/American Heart Association Task Force on Practice Guidelines. Committee to Update the 1997 Exercise Testing Guidelines. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation. 2002; 106:1883-92.
5. Pearson T A. New tools for coronary risk assesment: what are the their advantages and limitations? Circulation 2002; 105:886-92.
6. Khot UN, Khot MB, Bajzer CT, Sapp SK, Ohman EM, Brener SJ, Ellis SG, Lincoff AM, Topol EJ. Prevalence of conventional risk factors in patients in coronary heart disease. JAMA 2003; 290:898-904.
7. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2004; 27(Suppl 1):S1-S10.
8. Wilson PW, De Aagostino RB, Levy D, Belanger AM, Silbeshatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation 1998; 97:1837–47.
9. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, Douglas PS, Faxon DP, Gillam LD, Kimball TR, Kussmaul WG, Pearlman AS, Philbrick JT, Rakowski H, Thys DM, Antman EM, Smith SC Jr, Alpert JS, Gregoratos G, Anderson JL, Hiratzka LF, Faxon DP, Hunt SA, Fuster V, Jacobs AK, Gibbons RJ, Russell RO; ACC; AHA; ASE. 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Soc Echocardiogr 2003; 16:1091-110.
10. Pearson T A. New tools for coronary risk assessment: what are the their advantages and limitations? Circulation 2002; 105:886-92.
11. Feinstein SB, Voci P, Pizzuto F. Noninvasive Surrogate Markers of Atherosclerosis. Am J Cardiol 2002; 89(Suppl):31C–43C.
12. Leary DH, Polak JF. Intima-media thickness: a tool for atherosclerosis imaging and event prediction. Am J Cardiol 2002; 90 (Suppl):18L–21L.
13. De Boeck BW, Oh JK, Vandervoort PM, Vierendeels JA, van der Aa RP, Cramer MJ. Colour M-mode velocity propagation: a glance at intra-ventricular pressure gradients and early diastolic ventricular performance. Eur J Heart Fail 2005; 7:19-28.
14. Karaeren H, Erinç K, Uzun M, Demirtaş E. The importance of left ventricular early filling flow propagation velocity in prediction of pulmonary capillary wedge pressure: a comparative study with simultaneous invasive method. MN Kardiyoloji 1999; 6:325-8.
15. Garcia MJ, Smedira NG, Greenberg NL, Main M, Firstenberg MS, Odabashian J, Thomas JD. Color M-mode Doppler flow propagation velocity is a preload insensitive index of left ventricular relaxation: animal and human validation. J Am Coll Cardiol 2000; 35:201-8.
16. Boutouyrie P. Arterial ageing and coronary artery disease: physiopathological and epidemiological data. Arch Mal Coeur Vaiss 2006; 99:19-24.
17. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med 2000; 342:836-43.
18. Alan S, Ulgen MS, Ozturk O, Alan B, Ozdemir L, Toprak N. Relation between coronary artery disease, risk factors and intima-media thickness of carotid artery, arterial distensibility, and stiffness index. Angiology 2003; 54:261-7.
19. Bots ML, Hofman A, Grobbee DE. Increased common carotid intima-media thickness. Adaptive res-

ponse or a reflection of atherosclerosis? Findings from the Rotterdam Study. Stroke 1997; 28:2442-7.
20. Pontremoli R, Leoncini G, Ravera M, Viazzi F, Vettoretti S, Ratto E, Parodi D, Tomolillo C, Deferrari G. Microalbuminuria, cardiovascular, and renal risk in primary hypertension. J Am Soc Nephrol. 2002; 13(Suppl 3):S169-72.
21. Uzun M, Koz C, Yokusoglu M, Yildirim M, Baysan O, Erinc K, A novel marker of atherosclerosis; aortic flow propagation velocity. Eur J Clin Invest 2006; 36:286.
22. Gullu H, Erdogan D, Caliskan M, Tok D, Yildirim E, Ulus T, Turan Sezgin A, Muderrisoglu H. Interrelationship between noninvasive predictors of atherosclerosis: transthoracic coronary flow reserve, flow-mediated dilation, carotid intima-media thickness, aortic stiffness, aortic distensibility, elastic modulus, and brachial artery diameter. Echocardiography 2006; 23:835-42.

ORIGINAL ARTICLE

Does epidural clonidine improve postoperative analgesia in major vascular surgery?

Jelena Vuković[1], Papanna Ramakrishnan[2], Zoka Milan[2]

[1]Cardiovascular Institute of Dedinje, Belgrade, Serbia, [2]Leeds Teaching Hospitals, St James's University Hospital, Leeds, United Kingdom

ABSTRACT

Aim To determine the quality and duration of the analgesic and haemodynamic effects of clonidine when used as an additional analgesic for postoperative epidural analgesia in major vascular surgery.

Methods The prospective, single-blinded study involved 60 patients randomised into three groups (20 patients each): Group BM—bupivacaine 0.125% and morphine 0.1 mg/ml; Group BC—bupivacaine 0.125% and clonidine 5 μg/ml; Group MC—morphine 0.1 mg/ml and clonidine 5 μg/ml continuously infused at 5 ml/h. The quality and duration of the analgesia measured by the Visual Analogue Scale (VAS) at rest and on movement, additional analgesia requirements, sedation scores, haemodynamic parameters and side effects (respiratory depression, motor block, toxic effects, nausea and pruritus) were recorded.

Results The average VAS scores at rest and on movement were significantly lower in Group MC at two, six and 24 hours following the start of epidural infusion ($P<0.05$). The duration of the analgesic effect after finishing the epidural infusion was significantly longer in Group MC ($P<0.05$). Patients from Group MC were intubated longer. Additional analgesia consumption, sedation scores and haemodynamic profiles were similar in all three groups. Pruritus was more frequent in morphine groups ($P<0.05$), but other side effects were similar in all three groups.

Conclusion Under study conditions, clonidine added to morphine, not 0.125% bupivacaine, provided significantly better pain scores at two, six and 24 hours following the start of epidural infusion and the longest-lasting analgesia following the discontinuation of epidural infusion. However, patients from the Group MC were mechanically ventilated longer than patients from other two groups. Continuous monitoring of the patient is necessary after the administration of clonidine for epidural analgesia.

Keywords: clonidine, bupivacaine, morphine, epidural analgesia, postoperative period

Corresponding author:
Zoka Milan
Leeds Teaching Hospitals, St James's University Hospital
Lincoln Wing, Beckett St, Leeds,
United Kingdom
E mail: Z.Milan@leeds.ac.uk

Original submission:
21 October 2011;
Accepted:
25 November 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):49-55

INTRODUCTION

Major aortic surgery is associated with massive blood loss and fluid shift, haemodynamic instability, frequent post-operative complications and multiorgan failure (1-3). Epidural analgesia is the preferred method for postoperative pain and can reduce postoperative morbidity and mortality (4). So far, there has been no consensus or evidence on a preferable agent and dosage for epidural analgesia. Local anaesthetics are considered the most efficient for pain treatment, but they can cause hypotension in this high-risk patient population. The use of adjuvant drugs in analgesic combinations improve the quality of the analgesia and reduce the side effects (5). Clonidine, an alpha (α)-2-Adrenergic receptor agonist is known to have analgesic, sedative, perioperative sympatholytic, anaesthetic-sparing and hemodynamic-stabilizing properties (6,7).

To test the effect of the addition of epidural clonidine on postoperative pain scores, additional analgesia requirements, haemodynamic stability and side effects, we added clonidine to bupivacaine or morphine and compared the outcomes in patients treated with bupivacaine and morphine (our standard analgesic regimen at the time of this study). Our hypothesis was that clonidin added to bupivacaine or morphine would provide superior analgesia compared with a local anaesthetic and morphine analgesia.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and was conducted at the Institute for Cardiovascular Diseases, Dedinje, Belgrade, Serbia, between June 2002 and June 2003.

Seventy patients scheduled to undergo elective major vascular surgery (aortic aneurism repair, aorto-bifemoral or aorto-biiliacal shunt) provided their written consent.

Exclusion criteria were inclusion in another study protocol, contraindications for epidural catheter placement, allergies to any of the study drugs, arrhythmias and atrio-ventricular blocks, renal or liver failure, advanced respiratory failure, increased intracranial pressure, epilepsy, neurological diseases hypothyroidism or Addison's disease and use of irreversible MAO inhibitors or moclobemid.

Anaesthesia

The patients were premedicated with petidin 10 mg, atropine 0.5 mg and midazolam 5 mg IM and thirty minutes later, a 16G epidural catheter (Epidural kit; Portex) was inserted at the Th12-L1 level. All patients had a test dose of 3ml of lignocaine 1% with adrenaline 1:100 000.

General anaesthesia was induced with a fentanyl 1–2 mcg/kg and thiopenton 2–3 mg/kg, followed by pancuronium 0.6 mg/kg to facilitate endotracheal intubation. All patients were mechanically ventilated using volume-controlled, positive-pressure ventilation. Anaesthesia was maintained with sevoflurane at a 0.8-1 minimal alveolar concentration (MAC) in a 50% oxygen and 50% nitrous oxide mixture. For analgesia, four consecutive 5 ml boluses of 0.25% bupivacaine were administered. Additional analgesia included bolus doses of fentanyl, 1 μg/kg if the mean arterial pressure (MAP) or heart rate increased more than 20% from the baseline level. For muscle relaxation, 1 mg boluses of pancuronium were used.

Clinical monitoring included electrocardiography (ECG), pulse oximetry, invasive blood pressure and central venous pressure measurement, end-tidal carbon dioxide partial pressure, urine output and body temperature. Ephedrine 10 mg boluses were used to maintain the MAP above 65 mmHg.

Residual muscle relaxation was antagonised with atropine and neostigmine. Not all patients were extubated in the operating room. The postoperative analgesic regimen commenced with a 5-mL bolus of a pre-prepared mixture inserted via the epidural catheter when the Visual Analogue Scale (VAS) at rest was ≥3 or VAS at movement was ≥5. In sedated and mechanically ventilated pain was assessed on the basis of increased arterial pressure, heart rate, onset of arrhythmia, grimacing, movements, tears, sweating, breathing pattern and agitation.

The bolus was followed by a continuous infusion at a maximum of 5 mL/h. The infusion rate was kept between 2 mL/h and 5 ml/h and adapted to the patients' pain intensity, haemodynamic stability and side effects. The duration of the infusion was 24 h.

All patients were given standard cristaloid maintenance fluids. Colloids and blood transfusions were given if required. Ranitidine and low-molecular weight heparin were administered as per the Intensive Care Unit (ICU) protocol.

Rescue analgesia—2mg of morphine IV—was applied when the VAS score at rest was >3 and/or >5 at movement. When the infusion was discontinued 24 h after surgery, the time from discontinuation of the infusion to a new request for analgesia was measured.

Randomization in the study

One hour before the end of the surgical procedure, the patients were randomised prospectively to three groups using cluster randomisation until each group contained 20 patients: Group BM - Bupivacaine 0.125% and morphine 0.1 mg/ml, Group BC: Bupivacaine 0.125% and clonidine 5 μg/mL, and Group MC: Morphine 0.1 mg/mL and clonidine 5 μg/mL.

Additional exclusion criteria applied during the surgical procedure were technical difficulties in placing the epidural catheter, hypotension defined as MAP<65 mmHg and hypertension defined as MAP >135 mmHg.

A clinical pharmacist who was not involved in the direct clinical care of the patients prepared the epidural solutions in 50-ml syringes and labelled them with different coloured stickers. This same individual measured VAS and recorded haemodynamic parameters and side-effects during the first six postoperative hours. Trained nurses and junior doctors continued with the measurements and recordings up to 24 h after surgery.

Sedation was assessed by using Brussels' Sedation Scale (8): Level 1 was an unrousable patient, Level 2 was a patient who responds to pain stimulation (trapezius muscle pinching) but not to auditory stimulation, Level 3 was a patient who responds to auditory stimulation, Level 4 was a patient who is awake and calm and Level 5 was an agitated patient.

Side effects were recorded at regular time intervals: hypotension (MAP<65mmHg), bradicardia (HR<55/min), respiratory depression (respiratory rate <8/min and/or PCO_2>7KPa), nausea, pruritus, motor block and toxic effects.

Based on our previous pilot study of five patients, to detect a difference in a postoperative VAS score of 0.2 with a significance level of 0.05 and power of 80%, 20 patients in each group sufficed.

Statistics

Statistical analysis was performed using a statistical software package (SAS Version 9, SAS Institute, Cary, N.C.). Blood pressure, heart rate, and pain scores at rest and during movement were analysed using a one-way analysis of variance (ANOVA) for repeated measures. T test was used to evaluate differences between groups. Statistical significance was assumed at $p < 0.05$.

RESULTS

Seventy patients were included in the study. During randomisation, four patients were excluded because three had persistent bradycardia following surgery and one had hypertension before the start of the epidural analgesia. Two patients from the BM Group were excluded from the study because one had surgical complications and underwent another operation within 24 hours. Three patients from the BC Group were excluded because one developed postoperative acute renal failure requiring continuous veno-venous haemofiltration.

Sixty patients completed this study. The demographic and intraoperative data of our patients are shown in Tables 1 and 2. There were no significant

Table 1 Patients' from the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups

	Patients' group			
	Group BM	Group BC	Group MC	Statistical significance
Age (year)	60.9±8.6	61.5±7.9	59.5±6.5	NS
Weight (kg) Height (cm)	71.0±8.1 171.0±20.1	68.2±9.4 169.2±19.1	68.9±11.11 72.1±21.0	NS
Males/females ratio	15/5	16/4	15/5	NS
ASA III/IV	14/6	15/5	16/4	NS

NS, non significant

Table 2. Pre-op and post-op haemodynamic and anaesthetic data of patients in the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups

	Patients' group			
	BM	BC	MC	Statistical significance
Pre-op mean pressure (mmHg)	101.4±8.4	100.2±10	99.8±9.3	NS
Pre-op heart rate (beat/min)	73±9	74±10	75±8	NS
Post-op mean pressure (mmHg)	91.3±11.8	91.7±12.9	91.5±9.4	NS
Post-op heart rate (beat/min)	66±12	65±14	66±15	NS
Duration of anaesthesia (min)	173.5±46.9	170.7±48.2	173.2±44.3	NS
Intubated/ extubated ratio in ICU	10/10	12/8	12/8	NS

NS, non significant; ICU, Intensive Care Unit;

differences between the groups in terms of age, height, weight, American Society of Anesthesiologists (ASA) status, duration of anaesthesia, pre- and post-operative mean arterial blood pressure and heart rate. A similar proportion of patients were extubated at the end of their surgical procedures.

Patients required post-operative epidural analgesia 5–60 min following ICU admission (21.7±18 vs. 21.2±16 vs. 22.0±15 min, respectively), and there were no differences between the groups regarding the timing of the analgesia requirement.

The average VAS score at rest prior to administration of the first epidural bolus at rest was 3.4±0.8 vs. 3.4±0.8 vs. 3.3±0.7 without any significant difference between the groups. However, the VAS score on movement (5.6±1.0 vs. 5.4±0.8 vs. 5.4±0.8) was statistically higher in the BM Group compared with Groups BC and MC ($F = 5.046$; $df = 2$, $p < 0.05$).

As shown in Table 3, pain at rest was significantly lower in the MC Group two, six and 24 h after the initiation of continuous epidural infusion; it was lower in the BC Group 12 h after the initiation of continuous infusion compared with Groups BM and MC. As shown in Figure 1, pain at movement followed the same pattern.

The rate of epidural infusion for patients from all three groups was 3.8±1, 3.5±1 and 3.8±1 ml/h, respectively. There was no significant difference between the groups.

An additional 2 mgs of IV morphine analgesia were required by four patients in Groups BM and BC and five patients in Group MC and additional sedation was required for three, four and three patients from Groups BM, BC and MC, respectively, with no significant difference between the groups.

As shown in Figure 2, patients from Group MC had significantly deeper sedation before the start of epidural analgesia ($F=6.1$; $df=2$, $P<0.05$), but this difference disappeared after two hours of epidural analgesia.

Table 3. Patients' Visual Analogue Svale (VAS) scores at rest at two, six, 12 and 24 hours after initiation of epidural infusion in the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups

	VAS±SD			
Group of patients	**VAS2±SD**	**VAS6±SD**	**VAS12±SD**	**VAS24±SD**
BM	0.9±1.0	0.9±0.9	0.7±0.8	0.6±0.7*
BC	0.8±0.7	0.8±0.8	0.6±0.8*	0.6±0.7
MC	0.5±0.9*	0.5±0.7*	0.8±1.0	0.3±0.7*
	p<0.05	p<0.05	p<0.05	p<0.05

* statistically significant

Time to extubation was 3.2 ± 3 h, 4.2 ± 4 h and 5.3 ± 5 h, and it was significantly longer in Group MC ($z=7.429$; $p<0.01$).

There was no significant difference between total amount of bupivacaine (120±31.3mg group BM vs. 112±32.5 mg group BC), morphine (9.7±2.5 mg group BM vs. 9.6±2.5 mg Group MC) and clonidine (448±129.8 μg Group BC vs. 478±125.4 μg Group MC) used.

The duration of analgesia was significantly longer in Group MC (9.3 ± 3.0, 7.3 ± 2.6 and 12.9 ± 3.1 h, respectively) compared with the other two groups ($z = 7.438$; $p < 0.01$).

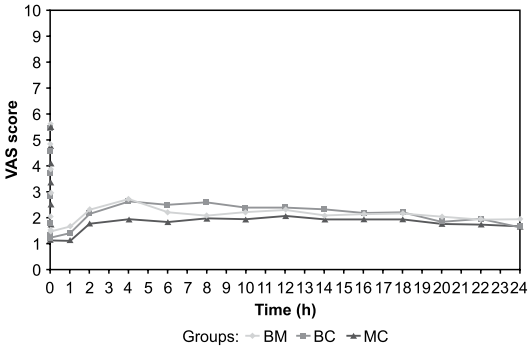


Figure 1. VAS scores in patients in the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups 24 h after the initiation of continuous epidural infusion

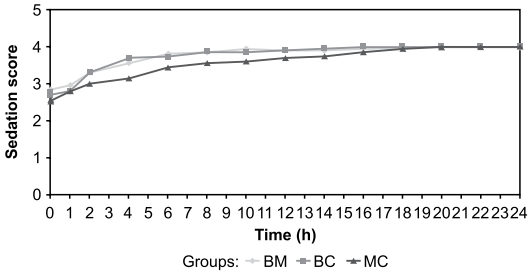


Figure 2. Sedation scores in patients in the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups 24 h after the initiation of continuous epidural infusion

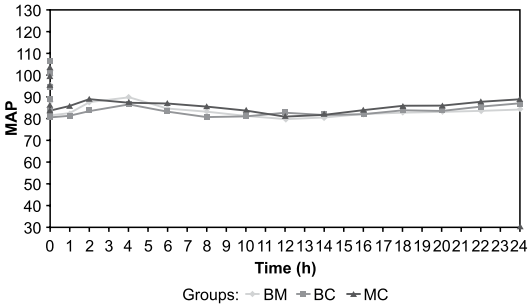


Figure 3. Mean arterial pressure (MAP) in patients in the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups 24 hours after the initiation of continuous epidural infusion

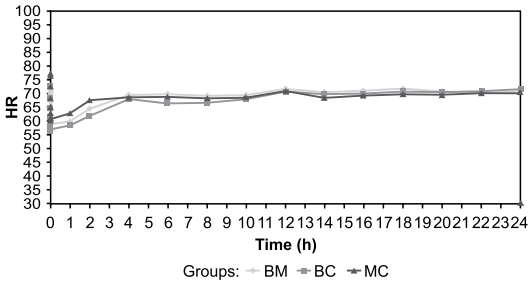


Figure 4. Heart rate (HR) in patients in the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups 24 hours after the initiation of continuous epidural infusion

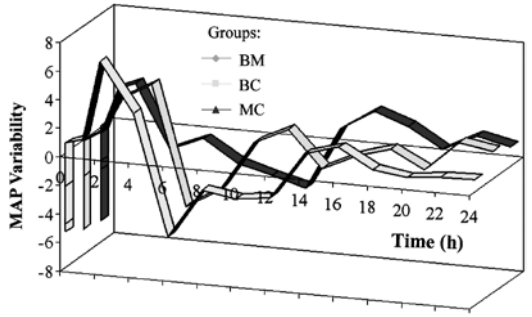


Figure 5. Mean arterial pressure (MAP) variation in patients in the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups 24 hours after the initiation of continuous epidural infusion

There were no significant differences in the mean arterial pressure and heart rate among the groups in all measured time intervals (Figures 3, 4, 5).

Table 4 presents the side effects of epidural analgesia during the study period. Pruritus was more present in patients from MC group when compared with BC group, and the difference was statistically significant (χ^2=3.8; df=2, P<0.05). Toxic effects were not noticed in any patient.

Table 4. Side effects during the study period in the bupivacaine and morphine (BM), bupivacaine and clonidine (BC) and morphine and clonidine (MC) groups

	Number of patients in the group		
Side effect	**BM**	**BC**	**MC**
Hypertension	5	1	4
Hypotension	3	3	2
Bradicardia	6	6	4
Respiratory depression	3	1	3
Nausea	5	5	5
Pruritus	3	0	4
Motor block	1	2	0

DISCUSSION

This was single-blinded, randomised, controlled trial comparing three different regimens of epidural analgesia following vascular surgery. Our study has shown that morphine and clonidine epidural analgesia provided significantly lower pain scores on hours two, six and 24 and longer lasting analgesia when compared with bupivacaine and clonidine or bupivacaine and morphine analgesia. However, patients who had clonidine and morphine for analgesia were extubated significantly later than patients who had clonidine and bupivacaine or morphine and bupivacaine.

Haemodynamic profile, additional analgesia and sedation were similar in all three groups. Pruritus was more frequent in morphine groups (P<0.05) but other side effects, named hyper and hypotension, respiratory depression, nausea, motor block and toxic effects were similar in all three groups.

Specific demand for epidural analgesia for vascular patients is to keep cardiovascular stability and achieve maximal analgesic effect with minimal dosage and side effects. The choice of dose and concentration of local anaesthetic solutions for epidural pain relief in vascular surgery are arbitrarily chosen . In order to keep the dose low, opioids were added for synergistic analgesic effect and better cardiovascular stability. However, opioids have side effects such as respiratory depression, pruritus and nausea and vomiting (9). For this study, we used a morphine dosage that we routinely use with 0.125% bupivacaine for postoperative epidural analgesia. In the current literature, doses of morphine used as an adjuvant to local anaesthetics are 0.05 to 0.2 mg/ml (10-12).

Clonidine, an alpha (α)-2-Adrenergic receptor agonist, has also been used as additive to local anaesthetics for vascular surgery patients and as a desirable sedative, bronchodilation and hemodynamic-stabilizing properties (6,7). In the current literature, doses of clonidine of 15mcg/h–150 mcg/h are used for continuous epidural adjuvant analgesia (13-16).

Clonidine has a direct local anaesthetic effect on nerve fibres, but there is also a synergistic effect between clonidine and opioids through delta opioids receptors (17,18). Clonidine's effect is increased to the threshold of a nociceptive stimulus, while morphine decreases in intensity of response to nociceptive stimuli (19). Although we used a low infusion rate (up to 5mL/h) for the analgesic solution, and combined a local anaesthetic with morphine and clonidine, we could not avoid

side effects. With all three analgesic combinations, we could not avoid nausea that was present in 25% of patients in all groups. We expected less nausea in the clonidine group (5). Time to extubation was the longest in Group MC.

One of limitations of this study was a constant need for local anaesthetic titration, additional analgesia boluses and additional sedation boluses. Our patients were very sensitive and required constant follow-ups and minimal changes in dosing. Involvement of two analgesic drugs through epidural infusion and additional analgesic and sedative agents make data interpretation and conclusion difficult. However, this was a real-life scenario in a dedicated vascular level II/III care unit.

We did not record average blood loss and patients' temperature for the purpose of this study, but by knowing the way we were warming our patients, we are sure that their temperatures were far below normal and therefore patients stayed intubated longer for the sake of warming. Low temperatures influenced drug metabolism and, consequently, pain scores.

Also, we waited for pain to occur in order to administer an epidural. From the current point of view, it might be unethical, but at the time when this study was conducted it was the way we were dealing with postoperative pain on daily basis and we had an ethics committee's approval for this study. Dosages of morphine and clonidine were arbitrary. To our knowledge, the equipotent doses of these two analgesics are not discovered.

In conclusion, under the study conditions, morphine and clonidine provided superior analgesia following major vascular surgery in terms of lower pain scores and longer durations of analgesia. However, it took longer to extubate patients whose analgesic regimen included morphine and clonidine. Haemodynamic effects and side effects, apart from pruritus that was more prominent in morphine groups, were similar in all three groups. This randomised controlled trial added data regarding optimal analgesia for vascular surgery patients. Further studies are needed to confirm the optimal local anaesthetic dosages and additives that can improve analgesia and minimise side effects.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Troisi N, Pulli R, Dorigo W, Lo Sapiro P, Pratesi C. Preoperative cardiac assessment in patients undergoing major vascular surgery. Vascular 2011; 19:178-86.
2. Muehling BM, Ortlieb L, Oberhuber A, Orend KH. Fast track management reduces the systemic inflammatory response and organ failure following elective infrarenal aortic anaurysm repair. Interact Cardiovasc Thorac Surg 2011; 12:784-8.
3. Ballotta E, Da Giau G, Militello C, Terranova O, Piccoli A. Major elective surgery for vascular disease in patients aged 80 or more: perioperative (30-day) outcomes. Ann Vasc Surg 2007; 21:772-9.
4. Muehling MB, Meierhenrich R, Thiere M, Bischoff G, Oberhuber A, Oren KH, Sunder-Plassmann L. The retroperitoneal approach combined with epidural anesthesia reduces morbidity in elective infrrenal aortic aneurysm repair. Interact Cardiovasc Thorac Surg 2009; 8:35-9.
5. Muehling B, Scheizig H, Steffen P, Meierhenrich R, Sunder-Plassmann L, Orend KH. A prospective randomized trial comparing traditional and fast-track patiet care in elective open infrarenal aneurysm repair. World J Surg 2009; 33:577-85.
6. Syal K, Dogra R, Ohri A, Chauhan G, Goel A. Epidural labour analgesia using bupivacaine and clonidine. J Anaesthesiol Clin Pharmacol 2011; 27:87-90.
7. Chan AK, Cheung CV, Chong YK. Alpha-2 agonists in acute pain management. Expert Opin Pharmacother 2010; 11:2849-68.
8. Detriche O, Berre J, Massaut J, Vincent JL. The Brussels sedation scale: use of a simple clinical sedation scale can avoid excessive sedation in patients undergoing mechanical ventilation in the intensive care unit. Br J Anaesth 1999; 83:698-701.
9. Bronstein I, White I, Ekstein MP, Brill S, Chazan S, Ogorek D, Ben-Abraham R, Amar E, Weinbroum AA. Higher postoperative pain and increased consumption follow pre-rather than post-incisional single dose epidural morphine. Minerva Anaesthesiol 2011; 77:408-17.
10. Pintaric TS, Potocnik I, Hadzic A, Stupnik T, Pintaric M, Jankovic VN. Comparison of continuous thoracic epidural with paravertebral block on perioperative analgesia and hemodynamic stability in patients having open lung surgery. Reg Anesth Pain Med 2011; 36:256-60.
11. Huang YS, Lin L, Huh BK, Sheen MJ, Yeh CC,

Wong CS, Wu CT. Epidural clonidine for postoperative pain after total knee arthroplasty: a dose-response study. Anesth Analg 2007; 5:1230-5.
12. Singh R, Kumar N, Singh P. Randomized controlled trial comparing morphine or clonidine with bupivacaine for caudal analgesia in children undergoing upper abdominal surgery. Br J Anaesth 2010; 106:96-100.
13. Rockemann MG, Seeling W, Brinkmann A, Goertz AW, Hauber N, Junge J, Georgieff M. Analgesic and hemodynamic effects of epidural clonidine, clonidine/morphine and morphine after pancreatic surgery- a double –blind study. Anesth Analg 1995; 80: 869-74.
14. Gottschalk A, Freitag M, Steinacker E, Kreissl S, Rempf C, Staude Hj, Strate T, Standl T. Pre-incisional epidural ropivacaine, sufentanil, clonidine, and (S)+-ketamine does not prove pre-emprive analgesia in patients undergoing major pancreatic surgery. Br J Anaesth 2008; 100:36-41.
15. Dobrydnjov I, Axelsson K, Gupta A, Lundin A, Holmstrom B, Granath B. Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: a double-blind randomized and placebo-controlled study. Acta Anaesthesiol Scand 2005; 49:538-45.
16. Olivier JF, Le N, Choiniere JL, Prieto I, Basile F, Hemmerling T. Comparison of three different epidural solutions off-pump cardiac surgery; pilot study. Br J Anaesth 2005; 95: 685-91.
17. Wolf M, Heugel P, Hempelmann G, Schoiz A, Muhling J, Olschewski A. Clonidine reduces the excitability of spinal horn neurones. Br J Anaesth 2007; 98:353-61.
18. Murata K, Nakagawa J, Kameta Y. Intrathecal clonidine suppresses noxiously evoked activity of spinal wide dynamic range neurons in cats. Anaesth Analg 1989; 69: 185-91
19. O'Meara ME, Gin T. Comparison of 0.125% bupivacaine with 0.125% bupivacaine with clonidine as extradural analgesia in the first stage of labour. Br J Anaesth 1993; 71:651-6.

ORIGINAL ARTICLE

Surgical treatment of patients with penetrating chest injuries sustained in war

Jozo Kristek, Krunoslav Šego, Borislav Has

Department of Surgery , University Hospital, Osijek, Croatia

ABSTRACT

Aim To show our experience in treatment of patients with penetrating chest injuries sustained during the Homeland War in Croatia.

Methods It was a retrospective study based on the records of the Department of Surgery of the University Hospital of Osijek (Croatia). All patients surgically treated during the wartime period (1991.-1995.) were analysed with respect to death rate, causes of injuries, frequency of injuries of thoracic organs and frequency of combined injuries of thorax and abdomen. Most of our patients were treated with thoracotomy as opposed to the common protocol (thoracostomy) applied in usual treatments.

Results The study includes 157 patients with penetrating chest wounds, 111 (70.7%) of which were from metal fragments of bursting artillery, 37 (23.6%) of the wounded were exposed to gunshot bullets, and 9 (5.7%) had stab injuries. Lung injuries had 134 (85.4%) patients, and15 (9.6%) had injuries of the heart. Chest injuries combined with injuries of abdominal organs happened in 30 (19%) cases. The abdominal organs in question were the liver, spleen, stomach, and colon, in eight (26.6%), seven (23.3%), four (13.3%), and three (10.0%) cases, respectively. Thoracotomy was performed in 144 (91.7%) cases, 13 (8.3%) of the patients underwent thoracostomy, and 134 (85.3%) patients stayed alive.

Conclusion It points out that, in our case due to organizational problems, aggressive surgical procedure of patients with penetrating chest and multiple injuries sustained in war was the good choice.

Key words: diaphragm, thoracotomy, thorax, wounds, penetrating

Corresponding author:
Krunoslav Šego
Department of Surgery,
University Hospital Osijek
J. Huttlera 4, 31 000 Osijek, Croatia
Phone: +385 31 511 511;
fax: +385 31 512 222;
E-mail: krunoslavsego@yahoo.com

Original submission:
01 April 2011;
Revised submission:
17 October 2011;
Accepted:
28 October 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):56-60

INTRODUCTION

Penetrating chest injuries sustained in war were mostly caused by powerful missiles with great kinetic energy bringing to extensive injuries of tissue and organs (1). This type of injury can be found in 28% of the total chest injuries (2). A significant percentage of penetrating chest injuries refers to combined injuries of thoracic and abdominal organs accompanied with injuries of anatomic compartment /diaphragm (hereinafter: combined thoracoabdominal injury). War experiences in Vietnam, Cambodia and Lebanon revealed frequent thoracotomy interventions within the surgical procedure for managing such penetrating chest injuries (3,4).

This study has shown the experience and treatment results of patients with penetrating chest injuries during the wartime period (1991-1995) treated at the University Hospital of Osijek, Croatia.

PATIENTS AND METHODS

It was a retrospective study based on the records of the Department of Surgery of the University Hospital of Osijek (Eastern Croatia). All patients surgically treated during the wartime period (1991.-1995) were analyzed with regard to death rate, causes of injuries, frequency of injuries of thoracic organs and frequency of combined injuries of thorax and abdomen.

After the triage, most of the casualties with penetrating chest injuries were admitted to the Department of Surgery. Due to wartime activities, poor transportation conditions and continuous bombing of the city and its surroundings, the surgical procedure used to start between 30 minutes and 2 hours after the occurrence of an injury. Many patients needed reanimation after clinical evaluation. Along with this procedure, routine laboratory analysis and a two-view radiological examination of the injured area (chest or/and abdomen) were performed. According to the military surgical doctrine, this was all supported by antitetanic prophylaxis and antibiotics treatment (combination of penicillin, gentamicine and metronidazole). The pellet pathway was judged according to the entrance wound and the position of the foreign object. Indications for thoracotomy were the following: clinical estimation of circulatory instability, X-ray findings of the hemato-pneumothorax and the amount of discharged/lost blood through the thoracic drain. The revision of the thoracic cavity was usually characterized by the anterolateral approach. Injuries of lungs were usually treated with sutures or by local debridement of devitalized tissue while in cases of extensive injuries, atypical resections were performed. Lobectomy or pulmonectomy was rarely an option. Foreign metal objects were removed only when they were reachable. Injuries of the heart were treated with a local suture and injuries of the main blood vessels with reconstructive procedure. An injury of the diaphragm was considered as an indication involving protrusion of abdominal organs in the thoracic cavity and signs of air in the left hypochondria. A rupture of the diaphragm was usually dealt with two-layer suturing. On rare occasions, the surgeons were forced to attempt reconstruction of a defect by using adjoining organs from the abdominal cavity such as the stomach.

A decision on the priority of a cavity was made prior to the surgery based on clinical evaluation and X-ray analysis. A number of patients with a combined thoracoabdominal injury underwent priority laparotomy, including safety expansion of the lungs with thoracic drain. Therefore, the patients subject to exploratory laparotomy as a part of penetrating thoracoabdominal wound treatment, even without demonstrated pneumothorax on chest roentgenogram, were recommended for preoperative tube thoracostomy to prevent the development of a tension pneumothorax during general anaesthesia.

The condition of acute abdomen in patients with a combined thoracoabdominal injury was usually diagnosed by means of clinical examination and radiological treatment. On very rare occasions when there was no time to carry out the entire procedure of peritoneal lavage, laparotomy was used to confirm the clinical evaluation. An injury of the small intestines was managed mostly with a local suture, resection was seldom the choice. An injury of the large intestines was dealt with mostly by oral derivation after a local suture or resection. A decision on the size of resection of the large intestines regarding combat injuries required rich surgical experience. After a local suture, the large intestines were seldom exteriorized, extraperitonealized or primarily anastomosed without oral derivation. Special attention was paid to stomach treatment. After debridement of a wound all the way to the healthy tissue and exact homeostasis, a two-layer suture was performed.

Spleen injuries were managed by spleenectomy while liver injuries were dealt with a local suture. Diagnosis of a kidney injury was mostly made by means of intra-operational revision of the abdomen. The surgical procedure of such injuries referred to a local suture of the wound and rarely to nephrectomy.

The postoperative care of a patient with a penetrating chest injury or/and a combined thoracoabdominal injury involved X-ray control of the chest as well as monitoring of respiratory and other parameters such as the amount of blood originating from both cavities and red blood count. Based on monitoring of the post-thoracotomy recovery course, one could say that even with satisfactory parameters there was a possibility of protracted postoperative hypotension as a consequence of protracted shock.

RESULTS

A group of 157 patients with penetrating chest injuries was observed. Most of them, 111 (70.7%), had injuries as a consequence of explosive artillery shells and metal shrapnel which were different in size and shape. Some were injured by gunshot bullets (23.6%, n=37), and few of them were stabbed with sharp objects (5.7%, n=9). With respect to the chosen surgical procedure, 144 (91.7%) thoracotomies, 13 (8.3%) thoracostomies, and 30 (19.1%) laparotomies were performed (Table 1).

Table 2 shows the frequency of injuries of particular organs of 157 patients with penetrating chest injuries accompanied with the appertaining treatment: 134 (85.4%) patients had lung injuries, and 15 (9.6%) heart injuries. Other involved organs were the bronchi, pulmonary artery and vein, subclavian artery and vein, azygos vein and innominate artery. The most frequent was a lung injury and the most popular treatment thereof was a local suture (104, 66.2%), followed by segmentectomy (21, 13.4%) and lobectomy (8, 5.1%).

Table 1. Causes of injuries in 157 patients with a penetrate chest injury and corresponding treatment protocol*

No (%) of patients according to			
Causes		**Treatment**	
Fragments of explosive artillery	111 (70.7)	Thoracotomy	114 (72.6)
Gunshot bullet	37 (23.6)	Thoracostomy	13 (8.3)
Stabbing with a sharp object	9 (5.7)	Thoracotomy + laparotomy	30 (19.1)
Total	157	Total	157

*frequency of thoracotomy is calculated as n =114/114+30 (72.6 %/19.1%)

Table 2. Frequency of injuries of particular organs in the chest area based on a group of 157 patients with penetrating injuries and appertaining treatment protocol

No (%) of patients			
Organ involved		**Treatment protocol**	
Lungs	134 (85.4)	lung suture segmentectomy lobectomy pulmonectomy	104 (66.2) 21 (1.4) 8 (5.1) 1 (0.6)
Heart	15 (9.6)	local suture	15 (9.6)
Bronchus	1 (0.6)	suture	1 (0.6)
Pulmonary artery and vein	2 (1.3)	reconstruction	2 (1.3)
Subclavian artery	2 (1.3)	reconstruction	2 (1.3)
Subclavian vein	1 (0.6)	reconstruction	1 (0.6)
Azygos vein	1 (0.6)	ligature	1 (0.6)
Innominate artery	1 (0.6)	reconstruction	1 (0.6)
Total	**157**		**157**

Table 3. Frequency of injuries of abdominal organs based on a group of 30 patients with a combined penetrate thoracoabdominal injury and accompanying treatment protocol

No (%) of patients			
Organ		**Providing protocol**	
Diaphragm	30 (100)	suture fundoplication	28 (93.3) 2 (6.7)
Liver	8 (26.6)	liver suture resection	6 (20) 2 (6.7)
Spleen	7 (23.3)	spleenectomy	7 (23.3)
Stomach	4 (13.3)	suture	4 (13.3)
Colon	3 (10,0)	suture + colostomy resection + solostomy	1 (3.3) 2 (6.7)
Small intestine	2 (6.7)	local suture	2 (6.7)
Pancreas	2 (6.7)	left pancreatectomy	2 (6.7)
Cystic duct	1 (3.3)	cholecystectomy	1 (3.3)
Portal vein	1 (3.3)	ligation	1 (3.3)
Right liver artery	1 (3.3)	ligation	1 (3.3)
Gall bladder	1 (3.3)	cholecystectomy	1 (3.3)

The diaphragm, liver, spleen and stomach (in 30, eight, seven and four cases) were most commonly injured (thoracoabdominal injury) (Table 3).

DISCUSSION

Penetrating chest injuries of patients treated during the Homeland War in Croatia were a result of exposure to bursting artillery, i.e. metal fragments of different sizes and shapes, in about 71% of cases. The basic characteristics of this kind of injury include major destruction along the pellet pathway and a possibly altered direction of the missile pattern. Our experience suggests that penetrating chest injuries (these also include peripheral parts of the lungs) lacked persuasive signs of hemato or/and pneumothorax in only several cases. Within a group of 157 survivors of penetrating chest injury, there was no combined injury of both thoracic cavities with a shrapnel

going through the centreline. This group of patients with a combined injury of the diaphragm and abdominal organs does not (n=30) include any single person with an injury of the aorta and vein cava. Only a few of them had problems with the pulmonary artery and vein, subclavian artery and vein, innominate artery or portal vein.

The study has revealed the perniciousness of injuries caused by larger shrapnel. The indication for thoracotomy in this study was similar to that of other authors (5-10). In this context, it should emphasize the difference in etiopathogenesis of the injuries. Most patients in this study were hit by metal shrapnel of explosive artillery, they were not stabbed with a knife or shot by a gunshot bullet as it usually happens in peacetime. The frequency of thoracotomy within the target group amounted to 91.7%. Thoracotomy as a result of a penetrating chest military injury was much less frequent (71%) during the warfare in Zachria, Lebanon (4). There was a relevant difference between the treatment protocol during the Lebanon war and the Homeland War in Croatia. Having been injured, patients were admitted to the hospital and underwent surgical treatment within a considerably shorter time in Lebanon in comparison with the admission time during the Homeland War in Croatia (4 min vs. 40-120 minutes). During the Lebanon war, the frequency of injuries caused by shrapnel from explosive artillery and by gunshot bullet totalled 57% and 42%, respectively (4). The patients from our target group suffered injuries from bursting artillery-related fragments in 71% of cases and from gunshot bullets in 24% of cases. In other words, our patients experienced more severe injuries and it took them more time to get to the hospital. Moreover, the Croatian examinees were more often diagnosed with circulatory instability and respiratory insufficiency as compared with Lebanese patients. Our results are specific because a great majority of the patients with the penetrating chest wounds were treated with thoracotomy as opposed to the common procedure (thoracostomy). Analysing our results it must be taken in consideration that the medical care was organized differently during the war in Croatia. The hospital was on the front line and it was impossible to predict the admission of the wounded on daily basis. We could not organize and plan evacuation of the wounded due to the war situation 2 km around the hospital, the city of Osijek was besieged and we had a dramatic lack of trained staff to monitor the wounded with the thorax drains (which is essential for thoracostomy procedure). Finally, indications for thoracotomy were found more frequently among our patients as compared to frequency in civilian practice and even in Lebanon war (4-10).

The mortality rate in our target group amounted to 14.7%. We think that the postoperative mortality was rather a consequence of adult respiratory distress syndrome (ARDS), squeezed lungs, postoperative ventilation-associated pneumonia and protracheal shock.

All of the examinees with a wound of the heart muscle and signs of cardiac tamponade had also small metal pieces in their bodies. As an attempt to temporarily stop bleeding, we used a finger or blown Fogarty balloons that we placed into the heart compartments. We have to emphasize that we did not have a cardiopulmonary bypass machine (11,12).

According to the results of this study the patients with combined thoracoabdominal injuries and accompanied injuries of the diaphragm were prioritized by indication of treatment sequence. As usual, the first step was performance of laparotomy with obligatory thoracic drain, which was constantly monitored by a team of anaesthesiologists. The most frequent injuries of abdominal organs in this group were liver, spleen and stomach injuries (13,14). Our experience indicates that with respect to isolated penetrating injuries of the abdominal cavity, the small intestines were the most endangered organs. Furthermore, our data suggest that the number of injuries of lower parts of the body and the extremities was larger than that of injuries of the upper parts of the body (15). Within the group of 30 patients with a combined injury of the thoraces and abdomen, the entrance wound was mainly positioned in the chest area. A comparison leads us to the conclusion that more pernicious injuries happened in cases of combined thoracoabdominal injuries, where the direction of injuring was abdomen>diaphragm>chest.

Management of the surgical procedure concerning the retroperitoneal region and organs (kidney) required rich experience. In such cases, cooperation with competent surgeons was necessary. The mortality rate of patients with kidney injuries mainly depended on existing abdominal injuries (16).

To sum up, a need for thoracotomy as a result of penetrating chest injuries was much more frequent in war practice than in peace, while the severity of military injuries of the same kind was without a parallel.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Mattox K, Pickard LM, Allen MK. Emergency thoracotomy for injury. Injury 1986; 17:327-31.
2. Howard IN, Ravdin IS. Surgery principles and practice. Philadelfia: Lipnicnot Company, 1957.
3. Fasd R, Zilla P, Irvine S, von Oppell V. Thoracoabdominal injuries in combat casualties on cambodian Borders. Thoracic Cardiovascular Surg 1988; 36: 33-6.
4. Zakharia AT. Thoracic battle injuries in the Lebanon war: review of the early operative approach in 1992 patients. Ann Thorac Surg 1985; 40: 209-13.
5. Oparah S, Mandal A. Operative management of penetrating wounds of the chest in civilian practise. Review of indications in 125 consecutive patients. J Thorac Cardiovasc Surg 1979; 77:162-168.
6. Aihara R, Millham F, Blansfield J, Hirsch E. Emergency room thoracotomy for penetrating chest injury: effect of an institutinal protocol. J Trauma 2001; 50:1027-1030.
7. Keel M, Meier C. Chest injuries - what is new? Curr Opin Crit Care 2007; 13(6):674-679.
8. Brown S, Gomez G, Jacobson L, Scherer T, McMillan R. Penetrating chest trauma: should indications for emergency room thoracotomy be limited? Am Surg 1996; 62:530-533.
9. Mattox KL. Indications for thoracotomy: deciding to operate. Surg Clin Nort Am 1989; 69:47-58.
10. Loogna PM, Bonanno F, Bowley DM, Doll D, Girgensohn R, Smith MD, Glapa M, Degiannis E. Emergency thoracic surgery for penetrating, non-mediastinal trauma. Journal of Surgery 2007; 77:142-5.
11. Čatipović-Veselica K, Sinčić V, Đurijanček J, Kozmar D, Burić D, Juranić B, Kristek J, Amidžić V. Penetrating heart wounds repaired without cardiopulmonary by-pass. Evaluation and follow-up of recent war injuries. Texas Heart Institute Journal 1993; 20: 94-8.
12. Seamon MJ, Shiroff AM, Franco MBS, Stawicki SP, Molina EJ, Gaughan JP, Reilly PM, Schwab CW, Pryor JP, Goldberg AJ. Emergency department thoracotomy for penetrating injuries of the heart and great vessels: an appraisal of 283 consecutive cases from two urban trauma centers. Journal of Trauma-Injury Infection & Critical Care 2009; 67:1250-8.
13. Kondža G, Kovačić D. Penetrating liver injuries sustained in war. Med Vjesn 1995; 27: 235-43.
14. Kovačić D, Lovrić Z, Kondža G. Military injures of the colon and rectum. Unfallchirurg 1994; 97:378-81.
15. Has B, Jovanović S, Wertheimer B, Mikolašević I, Grdić P. External fixation as a primary and definitive treatment of open limb fractures. Injury 1995; 26:245-8.
16. Kuveždić H, Tucak A, Grahovac B. Military injuries of the kidney. Injury 1996; 27:557-9.

Kirurško liječenje pacijenata s penetrantnim ratnim ozljedama prsnog koša

Jozo Kristek, Krunoslav Šego, Borislav Has

Klinika za kirurgiju, Klinički bolnički centar Osijek, Hrvatska

SAŽETAK

Cilj Prikazati iskustva u kirurškom liječenju ranjenika s penetrantnim ozljedama prsnog koša pretrpljenim za vrijeme Domovinskog rata u Hrvatskoj.

Metode Retrospektivnim istraživanjem, pacijenti koji su kirurški liječeni za vrijeme Domovinskog rata (1991.-1995.), analizirani su s obzirom na smrtnost, uzroke ozljede, učestalost ozljeda torakalnih organa i učestalost udruženih ozljeda toraksa i abdomena. Pacijenti ranjeni u prsni koš tijekom rata, u našoj bolnici većinom su liječeni torakotomijom za razliku od uobičajenog protokola liječenja (torakostomija).

Rezultati U studiju je uključeno ukupno 157 pacijenata: 111 (70,7%) osoba ozlijeđenih od ranjavanja krhotinama rasprskavajućih borbenih sredstava; 37 (23,6%) ranjenika ozlijeđenih puščanim zrnom; te 9 (5,7%) pacijenata s ubodnim ozljedama. Naime, 134 (85,4%) pacijenta imala su ozljedu pluća, a 15 (9,6%) ozljedu srca. Ozljede prsnog koša udružene s ozljedom abdominalnih organa nađene su kod 30 (19%) pacijenata. Najčešće ozlijeđivani abdominalni organi bili su jetra, slezena, želudac i debelo crijevo, u osam (26,6%), sedam (23,3%), četiri (13,3%) i tri (10%) slučaja. Torakotomija je učinjena kod 144 (91,7%), a torakostomija kod 13 (8,3%) pacijenata. Liječenje su preživjela 134 (85,3%) pacijenta.

Zaključci U zaključku naglašavamo da je u našem slučaju, s obzirom na organizacijske specifičnosti, agresivni kirurški tretman ranjenika s penetrantnim ozljedama prsnog koša bio dobar izbor liječenja.

Ključne riječi: ošit, torakotomija, prsni koš, rane, penetrantne

ORIGINAL ARTICLE

Exploring possibilities in nasal polyposis treatment at one Croatian hospital

Hrvoje Mihalj[1], Martina Mihalj[2], Željko Zubčić[1], Andrijana Včeva[1], Željka Laksar[1], Josip Maleš[1]

[1]Department of ENT and Head and Neck Surgery, Clinical Hospital Centre Osijek, [2]Department of Physiology and Immunology, Medical Faculty Osijek; Osijek, Croatia

ABSTRACT

Aim To validate different operative techniques commonly used for nasal polyposis (NP) treatment.

Methods This is a retrospective study exploring data on the NP surgery during a five-year period at the Ear, Nose and Throat Department at Clinical Hospital Centre Osijek, Croatia. Data were analysed regarding patients' gender, age, type of the surgery performed, and possible recurrence. Recurrence rate among patients that were followed up during that period of time and operated by different techniques (FESS vs. classical polipectomy) was compared.

Results Most frequently used operative technique was classical bilateral polypectomy, in 62.9% (154/245) of cases. The frequency of classical polypectomy was significantly decreased from 42/46 (91.3%) in 2006 to 34/60 (56.7%) cases in 2010, whereas the frequency of FESS in combination with classical polypectomy was significantly increased during that period ($p<0.0001$). Among patients with relapse that were followed up most of them were subjected to classical polypectomy at the time of their first surgery (9/10), thus implicating higher incidence of relapse in classically polypectomized patients.

Conclusion A higher incidence of recurrence in patients who underwent classical polypectomy implicates the need for additional precautions when choosing an operative technique. In addition, further investigation of NP and better understanding of etiology as well as the development of more specific drugs would be of great importance for the improvement of nasal polyposis treatment in the future.

Key words: nasal polyposis, FESS, polypectomy, therapy

Corresponding author:
Hrvoje Mihalj
Department of ENT and Head and Neck Surgery, Clinical Hospital Centre Osijek
Josipa Huttlera 4, 31000 Osijek, Croatia
Phone: +385 31 512 403;
fax.: +385 31 512 203;
E-mail: mihalj.hrvoje@kbo.hr

Original submission:
30 April 2011;
Revised submission:
04 October 2011;
Accepted:
03. November 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):61-65

INTRODUCTION

Nasal polyposis (NP) is a multifactorial disease of the lining of the nose and paranasal sinuses, characterized by the localized formation of benign growths on the mucous – polyps (1). Data on the prevalence and incidence of NP in Croatia are scarce. However, it appears in 1.4 to 4.3% of European population (2), mostly occurring between 30 and 60 years of age and with a clear male dominance. The ratio of male and female population affected by this disease is between 2:1 and 4:1 (3). NP presents a complex disease, perhaps even a common symptom of various entities. Everyday clinical practice keeps revealing obvious connection between NP and various chronic respiratory diseases, such as asthma, intolerance of aspirin and other non-steroidal anti-inflammatory drugs, cystic fibrosis, ciliary dysfunction, various syndromes, and chronic atopic and non-atopic sinusitis (4). In contrary, use of etiology-based therapy does not always help in reducing the symptoms and extent of NP (5). Years of studying have distinguished between several main theories, taking into account possible etiological factors, for example allergic, fungal, bacterial, obstructive, oxidative stress theory etc. (6). The main goal of NP treatment is to establish patency of the nose, recover the sense of smell and allow ventilation and drainage of paranasal sinuses. Conservative treatment is preferable to surgery and includes local and systemic steroids (5). In rare cases, where the etiology has already been proven, more specific therapies can be used (antibiotics, antifungal drugs, inhalations of diuretic furosemide, local application of capsaicin or interleukin antagonists etc) (7-12). There are two different surgical approaches to the treatment of NP: (1) classical polypectomy (removal of polyps from the nasal cavity) and (2) FESS - functional endoscopic sinus surgery (any sinus surgery undertaken with endoscopic control). The recurrence rate is affected by the operational radicality and the natural course of disease, but it seems that the latter plays an important role in the recurrence rate (13).

The main aim of this study was to determine the influence of different operative techniques on the incidence of recurrence in the patients who underwent surgery at the ENT Department at Clinical Hospital Centre Osijek during a five-year period (from 2006 to 2010). For that purpose only patients who underwent first surgery before 31December 2008 were used, as they had been followed up for at least 2 years. In addition, the frequency of certain techniques used, the rate of re-operation performed, and age and sex during the five-year period were analyzed.

PATIENTS AND METHODS

Study design

This is a retrospective study exploring data on the NP surgery during a five-year period (from 1 January 2006 to 31 December 2010). The data were collected from the official Register of Surgery at the Department of ENT and Head and Neck Surgery, Clinical Hospital Centre Osijek. All NP patients subjected to the surgery with afterwards proven benign NP were included into this study and information regarding their gender, age, type of the surgery performed, and possible recurrence of NP were collected.

Participants

All participants were patients suffering from NP that were subjected to surgery during their treatment at the Department of ENT and Head and Neck Surgery, Clinical Hospital Centre Osijek. Initially, they were examined by anterior rhinoscopy and underwent all standard laboratory diagnostics, including blood tests, nasal smear for eosinophils etc.

In all patients unsatisfactory response to intranasal corticosteroid sprays during a six-month therapy with persistent symptoms and reduced quality of life was an indication for performing the surgery. The patients were operated by FESS, classical polypectomy or combination of these two techniques by using Karl Storz operating equipment. The polypoid tissue removed during the surgery was sent to the Department of Pathology for immunohistochemical assessment. All cases of relapse that occurred in patients operated in the examined 5-year period had their first operation within the first three years (January 2006 to December 2008), and they could have been followed up for at least 2 years.

Statistics

Collected data were summarized in Microsoft Excel tables and the descriptive statistics were analysed by SPSS 16.0 software (SPSS Inc., Chicago, IL, USA). To compare among the groups

Chi-square test was utilized and the level of significance was set at $p<0.05$. The values are presented as mean ±S.E.M.

RESULTS

This study examined frequency of the nasal polyposis surgery at the Department of ENT and Head and Neck Surgery Clinical Hospital Centre Osijek during a five-year period (from January 2006 until December 2010). During that period 245 operations were recorded. Among the patients who underwent surgery, 155 (63.3%) of them were males and 90 (36.7%) females. The average for performed operations per year was 49±3.82 and did not vary significantly among the years studied (Table 1). Overall most frequent operative technique used during the examined 5-year period was classical bilateral polypectomy, in 154 (62.9%) cases. The frequency of classical polypectomy we used was significantly decreased from 42 (out of 46) (91.3%) in 2006 to 34 (out of 60) (56.7%) treated patients in 2010, whereas the frequency of FESS in combination with classical polypectomy was significantly increased during this period, from 0 (out of 46) (0%) in 2006 to 13 (out of 60) (21,6%) treated patients in 2010 (Figure 1). **The rate of FESS varied among the years, ranging from 4 (out of 46) (8.7%) to 13 (out of 60) (21,6%)** treated patients**.**

The polyposis recurrence rate was relatively high and was presented in 52 (21.2%) cases (Table 2). Among patients subjected to surgery because of reoccurring polyposis, only 10 (4,1%) of them had their first operation within the first three years of the period examined in this study (January 2006 to December 2008) and could have been

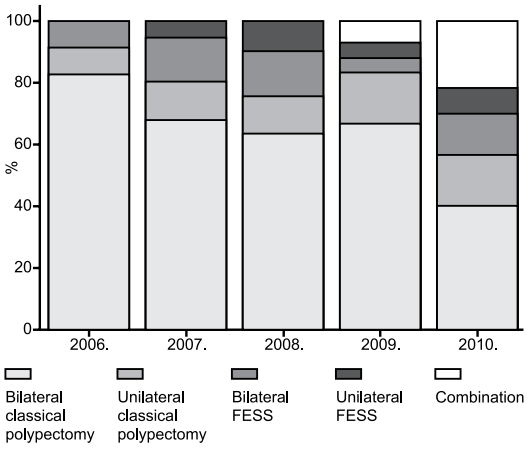


Figure 1. The frequencies of different types of operative techniques used among the years studied

Table 1. Frequency of nasal polyposis surgery

Year	Female	Male	Surgery/year
2006	10 (21.7%)	36 (78.3%)	46 (18.8%)
2007	19 (33.9%)	37 (66.1%)	56 (22.9%)
2008	18 (43.9%)	23 (56.1%)	41 (16.7%)
2009	16 (38.1%)	26 (61.9%)	42 (17.1%)
2010	27 (45.0%)	33 (55.0%)	60 (24.5%)
Total	90 (36.7%)	155 (63.3%)	254 (100.0%)

Table 2. Frequency of nasal polyposis relapses

	Number (%) of patients					
	2006	**2007**	**2008**	**2009**	**2010**	**Total**
First surgery	36 (78.3%)	45 (80.3%)	34 (82.9%)	34 (80.9%)	44 (73.3%)	193 (78.8%)
Relapse	8 (17.4%)	10 (17.9%)	4 (9.8%)	8 (19.1%)	12 (20.0%)	42 (17.1%)
Relapse during follow-up	2 (4.3%)	1 (1.8%)	3 (7.3%)	0 (0.00%)	4 (6.7%)	10 (4.1%)
Total	46 (18.9%)	56 (22.8%)	41 (16.7%)	42 (17.1%)	60 (24.5%)	245 (100.0%)

Table 3. Frequency of relapses compared between sex

	Number (%) of patients	
	Female	**Male**
First surgery	68 (75.6%)	125 (80.6%)
Relapse	20 (22.2%)	22 (14.2%)
Relapse during follow-up	2 (2.2%)	8 (5.2%)
Total	90 (36.7%)	155 (63.3%)

followed-up. In these patients the earliest relapse appeared after 2.5 months, and the average period for second occurrence of the polyps was 24±6 months. Majority of these patients were subjected to classical polypectomy at the time of their first surgery 9/10 (90%). The polyposis recurrence rate did not vary among the years studied ($p=0.600$) or the sex ($p=0.186$) (Table 2, Table 3).

DISCUSSION

The natural course of nasal polyposis and its treatment is highly variable. In some cases patients may be progression-free for many years while using intranasal steroids which are effective in preventing or delaying recurrence of nasal polyps. However, their effectiveness in delaying a need for repeated polypectomy in clinical practice is still unknown (14). On the other end of the spectrum there are patients with massive polyposis and strong supporting rhinosinusitis symptoms that respond poorly to medical therapy and rapidly re-occur after surgery. Fortunately the latter is relatively rare (15). Most patients fall somewhere between these extremes (15). This diverse and unpredictable course of the disease is quite frustrating for the patients and ENT surgeons. Therefore, numerous

studies have been conducted and aimed at finding prognostic factors for the outcome of NP (15). A problem rising in the follow-up of NP patients is not having "easy" and reliable biomarkers (16) from blood or locally available samples that would allow objective assessment of the disease severity and the outcomes of the therapy. In addition, there are no reliable biomarkers that would define the etiology in particular cases (16). These facts once more suggest the important role of basic research in conjunction with the ENT practitioners for the better understanding of the NP etiology and future improvement of the NP treatment.

Furthermore, several very important facts in regard to the therapeutic approach of NP patients should be stressed out at this point. First of all, it should be noted that not all histologically (17) proven recurrent polyposis patients require surgical re-treatment, especially if they can be maintained on conservative therapy with satisfactory results. Conservative treatment usually consists of intranasal corticosteroid spray (mometasone or fluticasone-furoate), or eventually by adding local corticosteroid drops over a short period of time. In severe cases oral corticosteroid therapy for several days could be effective as well (18). Secondly, when a local infection has been proven in the operated area local antibiotic therapies could be useful (19). Functional endoscopic sinus surgery is currently the most accepted surgical technique of NP and chronic rhinosinusitis worldwide (20). Our study revealed a significant improvement in regard to using FESS for the nasal polyposis surgery, but the dominant surgical approach at the ENT Department at Clinical Hospital Centre Osijek remains classical polypectomy. Consistent to the worldwide studies most patients who underwent nasal polyposis surgery were males (21). In our study 21.2% of all operated patients had relapse and were subjected to reoperation. Among the patients with relapse, that were followed up for at least 2 years, most of them were subjected to classical polypectomy at the time of their first surgery (9/10), thus implicating higher incidence of relapse in classically polypectomized patients. Unfortunately, lack of data from the period before 1 January 2006 made it impossible to have the data of a type of the operative technique at first surgery in 42 cases of relapses. Therefore, continuous assessment and follow-up in the future is needed to add significance to our findings. Recent epidemiological studies and scientific data favour endoscopic sinus surgery over polypectomy as well (20, 22). Percentage of overall complications was reported in only one comparative study and was 1.4% for FESS compared with 0.8% for conventional procedures (20, 22).

There is an evident tendency at the ENT Department at Clinical Hospital Centre Osijek to introduce FESS as first choice for surgical treatment of NP patients. Endoscopic approach allows excellent visibility of the deep structure with minimal invasiveness and at the same time preserves the function of the nose and paranasal sinuses. However, ENT surgeons at Clinical Hospital Centre Osijek as well as in other adjacent hospitals where classical polypectomy is still performed should be aware of all the advantages of introducing FESS in their hospitals for the benefit of their patients.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Fokkens W, Lund V, Bachert C, Clement P, Helllings P, Holmstrom M, Jones N, Kalogjera L, Kennedy D, Kowalski M, Malmberg H, Mullol J, Passali D, Stammberger H, Stierna P; EAACI. EAACI position paper on rhino sinusitis and nasal polyps executive summary. Allergy 2005; 60:583-601.
2. Fokkens W, Lund V, Mullol J. European position paper on rhinosinusitis and nasal polyps 2007. Rhinol Suppl 2007; 20:1-136.
3. Kirtsreesakul V. Update on nasal polyps: etiopathogenesis. J Med Assoc Thai 2005; 88:1966-72.
4. Samter M, Beers RF. Concerning the nature of intolerance to aspirin. J Allergy 1967; 40:281.
5. Holmberg K, Karlsson G. Nasal polyps: surgery or pharmachological intervention?. Eur Respir Rew 1994; 4:260-5.
6. Tos M. The pathogenic theories on the formation of nasal polyps. Am J Rhinol 1990; 4:51-6.
7. Kroflic B, Coer A, Baudoin T, Kalogjera L. Topical furosemide versus oral steroid in preoperative management of nasal polyposis. Eur Arch of Oto-Rhino-Laryngol 2006; 263:767-71.
8. Gotfried MH. Macrolides for the treatment of chronic sinuitis, asthma and COPD. Chest 2004; 125:52-61.
9. Ebbens FA, Scadding GK, Badia L, Hellings PW, Jorissen M, Mullol J, Cardesin A, Bachert C, van Zele TP, Dijkgraaf MG, Lund V, Fokkens WJ. Amphote-

ricin B nasal lavages: not a solution for patients with chronic rhinosinusitis. J Allergy Clin Immunol 2006; 118:1149-56.
10. Ponikau JU, Sherris DA, Weaver A, Kita H. Treatment of chronic rhinosinusitis with intranasal amphotericin B: a randomized, placebo-controlled, double-blindpilot trial. J of All & Clin Immunol 2005; 115:125-31.
11. Weschta M, Rimek D, Formanek M, Polzehl D, Podbielski A, Riechelmann H. Topical antifungal treatment of chronic rhinosinusitis with nasal polyps: a randomized, double-blind clinical trial. J Allergy Clin Immunol 2004; 113:1122-8-63.
12. Passali D, Bernstein JM, Passali FM, Damiani V, Passàli GC, Bellussi L. Treatment of recurrent chronic hyperplastic sinusitis with nasal polyposis. Arch Otolaryngol Head Neck Surg 2003; 129:656-9.
13. Grgić MV. Predictors of the effectiveness of nasal polyposis surgical treatment. PhD thesis. Zagreb, University of Zagreb, 2009.
14. Punekar YS, Ahmad A, Saleh HA. Estimating the effect of nasal steroid treatment on repeat polypectomies: survival time analysis using the General Practice Research Database. Rhinology 2011; 49:190-4.
15. Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. Laryngoscope 2004; 114:811-3.
16. Platt MP, Soler Z, Metson R, Stankovic KM. Pathways analysis of molecular markers in chronic sinusitis with polyps. Otolaryngol Head Neck Surg 2011; 144:802-8.
17. Van den Boer C, Brutel G, de Vries N. Is routine histopathological examination of FESS material useful? Eur Arch Otorhinolaryngol 2010; 267:381-4.
18. Schalek P, Petrás P, Klement V, Hahn A. Short-term antibiotics treatment in patients with nasal polyps and enterotoxins producing *Staphylococcus aureus* strains. Eur Arch Otorhinolaryngol. 2009; 266:1909-13.
19. Yaman H, Alkan N, Yilmaz S, Koc S, Belada A. Is routine histopathological analysis of nasal polyposis specimens necessary? Eur Arch Otorhinolaryngol 2011; 268:1013-5.
20. Dalziel K, Stein K, Round A, Royle P. Endoscopic sinus surgery for the excision of nasal polyps: A systematic review of safety and effectiveness. Am J Rhinol 2006; **20**:506-9.
21. Devars du Mayne M, Prulière-Escabasse V, Zerah-Lancner F, Coste A, Papon JF. Polypectomy Compared With Ethmoidectomy in the Treatment of Nasal Polyposis. Arch Otolaryngol Head Neck Surg. 2011; 137:111-117.
22. Dalziel K, Stein K, Round A, Garside R, Royle P. Systematic review of endoscopic sinus surgery for nasal polyps. Health Technol Assess 2003;7:iii:1-159.

Mogućnosti liječenja nosne polipoze u jednoj hrvatskoj bolnici

Hrvoje Mihalj[1*], Martina Mihalj[2], Željko Zubčić[1], Andrijana Včeva[1], Željka Laksar[1], Josip Maleš[1]

[1]Klinika za otorinolaringologiju i kirurgiju glave i vrata, Klinički bolnički centar Osijek; [2]Katedra za fiziologiju i imunologiju, Medicinski fakultet Osijek; Osijek, Hrvatska

SAŽETAK

Cilj Cilj istraživanja bio je ispitati učestalost i ishod različitih operativnih tehnika koje se koriste kod liječenja nosne polipoze (NP).

Metode Ovo je retrospektivna studija o kirurškom liječenju NP-a tijekom petogodišnjeg perioda na Klinici za uho, grlo i nos KBC-a Osijek (Hrvatska). Obuhvaćeni su svi pacijenti operirani zbog NP-a u tom periodu, te prikupljeni podaci o spolu, dobi, tipu primijenjene operacije i eventualnom relapsu bolesti. Kod pacijenata koji su bili praćeni tijekom tog razdoblja, uspoređena je učestalost pojave recidiva ovisno o primijenjenoj operativnoj tehnici.

Rezultati Klasična polipektomija bila je najčešće primjenjivana operativna tehnika 62,9% (154/245). Tijekom ispitivanog razdoblja zabilježen je značajni pad učestalosti klasične polipektomije, s 42/46 (91,3%) tijekom 2006. godine na 34/60 (56,7%) u 2010. godini, te porast učestalosti FESS-a u kombinaciji s klasičnom polipektomijom ($p<0,0001$). Među pacijentima s relapsom, koji su mogli biti praćeni tijekom promatranog razdoblja, većina ih je bila operirana klasičnom polipektomijom prilikom prve operacije (9/10), što sugerira veću incidenciju relapsa kod ove operativne tehnike.

Zaključak Viša incidencija recidiva kod bolesnika podvrgnutih klasičnoj polipektomiji implicira potrebu za povećanim oprezom pri odabiru operativne tehnike. Osim toga, suradnja između klinike i bazičnih medicinskih znanosti, daljnja istraživanja na području NP-a, bolje razumijevanje etiologije i razvoj specifičnijih lijekova, neophodni su za unapređenje liječenja nosne polipoze u budućnosti.

Ključne riječi: nosna polipoza, FESS, polipektomija, terapija

ORIGINAL ARTICLE

The efficacy of novel therapeutic modalities of isolated ocular vasculitis vs ocular vasculitis as a systemic disease

Gordana D. Zlatanović[1], Svetlana V. Jovanović[2], Maja LJ. Živković[1], Marko LJ. Zlatanović[1], Sunčica B. Srećković[2], Filip M. Radotić[3]

[1]Department for Retinal Disorders, Eye Clinic, Clinic Centre Niš, [2]Department for Retinal Disorders, Eye Clinic, Clinical Centre of Kragujevac, [3] Medical Faculty, University of Kragujevac, Kragujevac; Serbia

ABSTRACT

Aim To evaluate the efficacy of new therapeutic modalities with the observation period of three years on patients with isolated ocular vasculitis in comparison with ocular vasculitis as a systemic disease.

Methods The effectiveness of the therapy was assessed based on the changes in visual acuity and degree of ocular inflammation (mild, medium, moderate, severe) with the following parameters: vitreous body cloudiness, blood vessels layering, macula oedema, blood vessels occlusion and new vascularisation.

Results New therapeutic modalities resulted in reduction in the number of patients with severe inflammation in the group of isolated ocular vasculitis from 8(13.5%) to 7(12.2%) after three years, while the number of patients with mild inflammation increased from 13(20.7%) to 18 (29.3%) in the same group ($p>0.05$). The number of patients with severe ocular inflammation in a group of ocular vasculitis as systemic disease increased from 3(16.2%) to 4(21.6%), because of the presence of patients with Behçet's disease. The number of patients with visual acuity less than 0.1 decreased from 11(17%) to 8(13.4%) in a group of patients with ocular vasculitis as systemic disease, which was associated with the presence of Behçet's disease too ($p>0.05$).

Conclusion Although the effect of new therapeutic modalities did not result in statistically significant improvement in visual acuity and reducing inflammation, systemic and intravitreal corticosteroids with steroid-sparing immunomodulatory therapy represents effective strategies in forms of isolated ocular vasculitis and ocular vasculitis as systemic disease.

Key words: vaculitis, biological agents, immunomodulators.

Corresponding author:
Svetlana V. Jovanović
Department for Retinal Disorders,
Eye Clinic, Clinical Centre of Kragujevac
Zmaj Jovina 30,
34000 Kragujevac, Serbia
Phone: +381 63 302 555;
fax.: +381 34 370 151
E-mail: micaj034@yahoo.com

Original submission:
10 March 2011;
Revised submission:
13 May 2011;
Accepted:
29 August 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):66-73

INTRODUCTION

The term "ocular vasculitis" includes retinal vasculitis, choroid vasculitis, optic nerve vasculitis, papillitis, episcleritis, scleritis including peripheral ulcerative keratitis. Ocular vasculitis according to the classification of systemic vasculitis (1), caused by primary systemic vasculities and lesions caused by secondary systemic vasculities. Following this principle Herbot recommended that detailed classification of ocular vasculitis includes four main subclasses (2).

Ocular vasculitis is a refractory disease with frequent relapses and poor response to all available methods of therapy (2). The choice of therapy is defined by the severity of the illness. In cases where the disease is mild with good visual acuity, especially in unilateral forms of the disease, the observation of the patients without any therapy is recommended (3). In case of Eale's disease, however, or if new vascularisation is found, laser light coagulation is recommended. In more severe cases of inflammation systemic therapy is required (4). Generally, treatment should be more aggressive in cases when repeated bilateral ocular vasculitis occurs (5).

Systemic corticosteroids produce undeniably quick anti-inflammatory effects in all phases of disease, particularly in the acute phase (6). In chronic cases of the disease, maintaining doses of prednisolone might be administered in combination with antimetabolites such as methotrexate (MTX) (7,8) azathioprine, mycophenolate mofetil (9,10), calcineurin inhibitors which include cyclosporine (11), alkylating agents which include cyclophosphamide and chlorambucil. Immuno-modulatory agents are generally used in ocular vasculitis on patients with bilateral disease whose vision has fallen below 0.5 in the better eye (12). Now increasingly used biological agents in ocular inflammations include TNF-α inhibitors infliximab (13), adalimumab, etanercept and cytokine receptor antibodies (daclizumab), interferon-α (14-16).

The new therapeutic modalities allow high-doses of corticosteroids to be administered to the inside of the eye, by the use of implanted slow-release devices (17) or by direct intraocular injections (18,19). Direct intravitreal injected triamcinolone is most commonly used today, especially in vasculitis with ocular involvement, predominant ocular involvement or with unilateral ocular disease (20). The new therapeutic biological treatment against TNF-α can be given to patients who are intolerant or react to other disease modifying drugs (21,22).

Laser ablative therapy is applied in cases with neovascularisation and ischemic area as a consequence of vasculitis (23). Vitrectomy is of benefit to clear the area, when there is marked inflammatory debris and haemorrhage, and to remove epiretinal membranes (24).

The goal of this research was to show the effects of new therapeutic modalities carried out on two groups of patients with vasculitis, those with ocular vasculitis as isolated disease and those whose vasculits as a systemic disease, in the three years period.

PATIENTS AND METHODS

Clinical investigation was carried out in Clinic for Ophthalmology of the Clinical Center in Niš (Serbia) and Clinic for Ophthalmology of the Clinical Center in Kragujevac (Serbia) in the period of 2008-2010, on 82 patients with ocular vasculitis, of which 62 have had ocular vasculitis as isolated disease, and 20 of whom had ocular vasculitis as a systemic disease. Diagnostic methods for the diagnosis of systemic disease were according to protocol (25). Patients with serious hypertension or diabetes were not included in our investigation. Among the 82 patients, 119 eyes were treated.

This investigation included determination of the visual acuity of the patients on their first examination, and again after a three-year period. Also, on the first examination and again after three years, the seriousness of ocular disease was determined according to the following five criteria: vitreous body cloudiness, blood vessels layering, macula oedema, blood vessels occlusion and new vascularisation events. In accordance with this, all patients were divided into four groups, those with mild (less than 6 points), or medium (6 -10 points), or moderate (11- 20 points), or severe ocular disease (over 20 points). The choice of the therapy is determined by the intensity of illness.

For mild forms of the disease, where the patients had well-preserved visual acuity, the patients were monitored every two months. They are tailored

acording to any findings on hystory and examination. In the medium form of ocular vasculitis, local corticosteroids were used. In moderate or severe forms, the ocular blood vessels inflammation was managed using high methylprednisolone doses of 140-160 mg/day (a morning dose) during at least 5-7 days, decreasing then gradually to a maintaining dose of 15 – 30 mg/day (Table 1). In patients with severe bilateral ocular disease, cyclophosphamide in a dose of 50-100 mg/day was applied, together with cyclosporine of 4 mg/kg and prednisolone of 40 mg (Table 2).

Patients in the group where ocular vasculitis was associated with systemic involvement (such as the multiple sclerosis group) received systemic corticosteroid treatment (with an initial dose of 1mg/kg basis) or a mega dose of methylprednisolone (Table 2, Figure 1). Patients received corticosteroid-sparing agents – methotrexate or IFN (Interferon -β) therapy if necessary (Table 1).

The Behçet`s group of vasculitis in the group with moderate ocular disease were treated with systemic corticosteroids, and cyclosporine (2.5-5mg/kg) if necessary (Table 1, Figure 2). Infliximab agents were used in refractory cases in the group with severe ocular disease (5mg/kg doses). The sarcoidosis group was treated with systemic corticosteroid and methotrexate agents (Table 1).

Spondyloarthritis with HLA (human leukocyte antigen)-associated uveitis if it affected the vessels of the retina dramatically in group with severe activity were treated with systemic corticosteroids and laser photocoagulation of the neovascularisation and ischemic areas. Methotrexate was applied also in a dose of 7.5 to 25 mg weekly in steroid dependent course with relapses or intolerance in the same group.

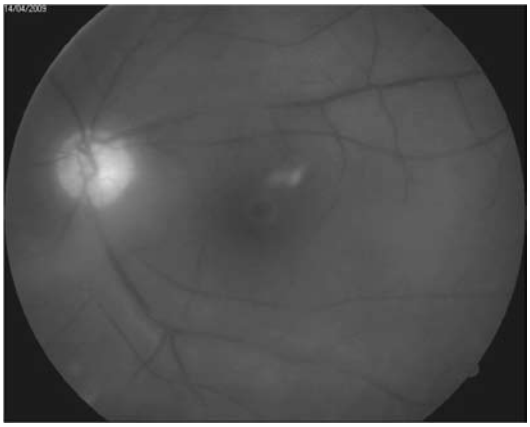


Figure 1. Fundus photography of patient with multiplex sclerosis disease showing phlebitis (Jovanović S., 2009)

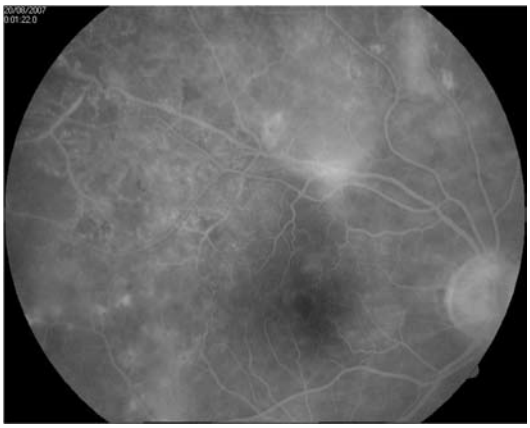


Figure 2. Fluorescein angiography of patient with Behçet's disease showing occlusive vasculitis, and microvascular leakage (Jovanović S., 2010)

Eale's disease, tuberculoprotein hypersensitivity vasculitis (hyper-positive tuberculin skin test present in these patients) was treated with systemic steroids, antituberculous therapy and full pan retinal photocoagulation (23).

With the pseudophacic patients with vasculitis in the group with moderate and severe ocular disease, intravitreal triamcinolone was applied in

Table 1. Therapy applied to these two groups of patients with ocular vasculitis as systemic disease and ocular vasculitis as isolated disease

Group of drug	Generic name	Doses	Adverse effects
Corticosteroid	Triamcinolone	Periocular:1 ml 20 mg/ml 0,5 ml 40 mg/ml Intravitreal: 4 mg/0.1 ml, 20 mg/0.2 ml	ocular pressure, cataracta
Corticosteroid	Prednisolone	1mg/kg day for 4-6 weeks, severe and moderate: 140-160 mg/day	
Corticosteroid	Methylprednisolone	0.5 - 1 gr/day pulse dose	
Calcineurin inhibitor	Cyclosporine A	2.5-5mg/kg/day	
Antimetabolites	Methotrexate	0.15 mg/kg /a week per os/scut/im	
Antimetabolites	Azathioprin	1-3 mg/kg/day p.er os	vomiting, diarrhea
Alkylating agents	Cyclophosphamide	1-3 mg/kg day per os, iv 750 do 1000 mg/ m sq every four weeks	bone marrow depression, vomiting
Biological product	Interferon ß Interferon α-2a	22 µg or 44 µg, three times a week daily s/cut 3-6 million IU	
Biological product	Infliximab	5mg/kg iv	autoimmune disease

Table 2. Distribution of patients with ocular vasculitis

	No (%) of patients with	
	Isolated ocular blood vessels inflammation vasculitis	Ocular vasculitis as systemic disease
Bilateral	20 (32%)	17 (85%)
Unilateral	42 (38%)	3 (15%)
∑82 (100%)	62 (75.6%)	20 (24.4%)

the dose of 20mg/0.2mL and 4mg/0.1 mL, depending on the severity of illness.

Early vitrectomy was performed in one five-year-old patient with phlebitis and rheumatoid arthritis in the group of moderate activity.

To calculate statistically significant differences between the groups, the SPSS 17.0 software package was used. Asymmetric distribution of frequencies resulting in the application of nonparametric analysis. Statistical analysis included the Wilcoxon signed ranks test. A level of statistical significance equals to or less than 0.05 indicated statistically significant difference. For non-parametric analysis Koen test influence on the criteria of the size was used: 0.1 small, 0.3 medium, 0.5 a large effect. For the distribution of the data among the groups tested the Shapiro-Wilk test used (for calculation of the difference from the normal distribution).

Ethical Committee of the Ministry of Health, the Republic of Serbia, approved this investigation. Patients had given their consent for inclusion in the research.

RESULTS

Over the period of three years 82 patients with ocular blood vessels inflammation were investigated, of which 53 (65%) were 20-40 years of age. No significant differences were found, with regard to the sex of the patients investigated.

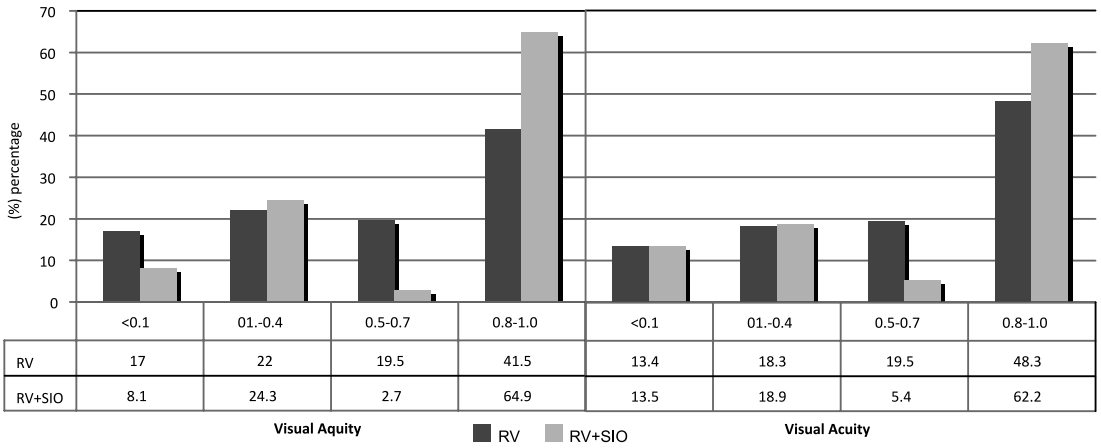


Figure 3. Visual acuity in observed groups on the first examination and after three years
RV, retinal vascutis; RV+SIO, retinal vasculitis with systemic inflammatory occurrences;

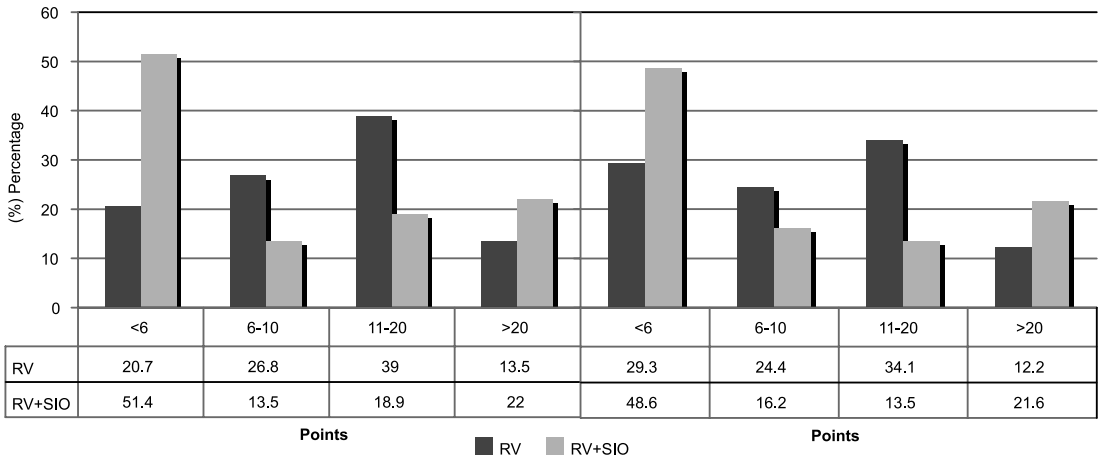


Figure 4. Seriousness of retinal vasculitis in observed groups on the first examination and after three years
RV, retinal vascutis; RV+SIO, retinl vsculitis with systemic inflammatory occurrences;

Ocular blood vessel inflammation was isolated in 62 (75.6%) and ocular vasculitis as a systemic disease in 20 (24%) patients.

Bilateral changes were found in 20 (out of the 62, 32%) patients with isolated ocular vasculitis, 17 (out of 20, 85%) patients were with ocular vasculitis associated with systemic disease (Table 2).

The highest number of patients with isolated ocular vasculitis had a moderate ocular disease, 24 (39%), and their visual acuity was 0.8-1.0 (Figure 3). The highest percentage of patients within the group with mild form of ocular vasculitis was associated with systemic disease, with visual acuity of 0.8-1.0 (Figure 3).

Half of the patients had mild or medium ocular disease, while the other half had moderate or severe ocular disease (Figure 4). At the end of the study, the number of patients with severe ocular disease and retinal blood vessel inflammation, as systemic disease, had risen from three (16.2%) to four (21.6%).

The three-year period of analysis of the patients, along with application of therapeutic modalities, has shown no statistically significant changes in the severity of the disease among the group of isolated ocular vasculitis ($p>0.05$) nor within the group of ocular vasculitis associated with any systemic disease ($p>0.05$). There was no statistically significant differences in severity between the two clinical groups of vasculitis before therapy application ($p>0.05$), nor after the therapy ($p>0.05$).

There was a reduction in the number of patients with severe ocular disease in the group of isolated ocular blood vessel inflammation, from 13.5% to 12.2%, after the period of three years. The percentage of patients with mild disease increased from 20.7% to 29.3% in the group with isolated ocular blood vessel inflammation (Figure 4).

Visual acuity was monitored on the first examination and after three years (Figure 3).

For light forms of the disease with well preserved visual acuity, only hygiene-dietary regime was recommended and the patients were controlled.

In patients with Eales disease, laser photocoagulation was applied successfully.

In medium retinal vasculitis, local midriatics and corticosteroids were used.

Significant difference in visual acuity was observed between the group of patients with isolated ocular vasculitis and ocular vasculitis as a systemic disease ($p=0.066$), but on the first examination it was not significant ($p>0.05$), and after three years of application of the therapy the difference was not statistically significant ($p=0.068$. Treatment did not result in significant improvement in visual acuity within the group with an isolated ocular vasculitis ($p>0.05$), nor in the group with ocular vasculitis as a systemic disease ($p>0.05$).

In 13 (64.9%) patients with ocular vasculitis as a systematic disease visual acuity was good, between 0.8 and 1.0. Visual acuity in the group of patients with isolated ocular blood vessel inflammation was worse, and was evenly distributed, in each observed group.

In the group of the patients with ocular vasculitis as a systemic disease, after the three-year period of curing, the number of patients with poor visual acuity increased from two (8.1%) to three (13.5%).

DISCUSSION

The application of new therapeutic modalities carried out on the group of patients with ocular vasculitis as isolated disease, and the group of patients with ocular vasculitis as systemic disease over the three-year period did not show significant improvement in clinical presentation nor visual acuity. Difference was noted within and between these groups but without statistical significance. The results of this study have shown an increasing trend of the patients with severe ocular disease in the group of ocular blood vessel inflammation as a systemic disease, which was probably associated with the presence of patients with Behçet's disease known to lead to blindness in 3.2 years if it was not treated, or in 7.4 years if it was treated (26). Novel therapeutic approach for Behçet's group of patients included the use of biological agents against TNF-α, infliximab in the dose of 5mg/kg (27). The application is limited by the cost and the uncertainty over long-term efficacy and safety (28). In our study biological agents were given to patients who were intolerant or who reacted to other medicaments. Immunosuppressive drugs are used to treat severe, mostly bilateral forms of inflammation, potentially blinding cases (29). Firstly, as corticosteroid-sparing therapy when the disease can be controlled with

oral corticosteroids, however, substantial toxicity would be expected at the dose required (30). Secondly, immunosuppressive drugs used for an inflammation that is resistant to corticosteroid (31), and finally, for management of specific diseases expected to fare poorly with corticosteroids alone (32). Cyclosporine A is generally limited to bilateral occurrences of ocular vasculitis which is a threat to sight, so it should be administered in less toxic doses in combination with corticosteroids (33). Methotrexate is an effective means of controlling uveitis on its own or in conjunction with other immunosuppressants (34, 39). It is popular a drug due to its low cost and high tolerability but does require baseline hepatitis serology as well as liver function tests, metabolic panel and complete blood count every two months (33).

Analysis of visual acuity parameters showed that after three years of follow up the improvement of vision occurred in both patient groups and isolated ocular vaslulitis and systemic vasculitis in the eye. The improvement of vision in both patient groups analysed in this study was noted, and it was greatest in patients with the best visual acuity. This could be explained according to a top-down model of treatment, i.e., early intervention with disease modifying agents, such as methotrexate, immunomodulatory agents, and now with biologic response modifiers (infliximab) (34). In patients with low visual acuity below 0.1 in the group of ocular vasculitis as systemic disease there was a decrease of visual acuity after three years of following, which is again associated with the presence of Bekçet's disease (35).

We believe that the application of intravitreal triamcinolone resulted in the decrease in the number of patients with poor visual prognosis. (18-20). Most of our patients had 1-3 relapses over the three-year period.

Although combining new therapeutic modalities with current treatments did not show a statistically significant improvement in clinical presentation and visual acuity of the patient with isolated ocular vasclitis and patients with ocular vasculitis as systemic disease, they did show an effect on progress and on the final outcome of the disease. The ''target treatment'' with minimal side effects is based on the improvement of the existing medication (such as intravitreal application of corticosteroids) together with better understanding of the mechanisms of autoimmune diseases (such as biological agents), as well as a better delivery system, (such as implants). Subsequent introduction of this new therapeutic procedure will in practice contribute greatly to an efficient non-toxic treatment of patients with ocular vasculitis.

FUNDING

This work supported by Grant No: 500-01-00035 from the Ministry of Health, the Republic of Serbia.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J,GrossWL, Hagen EC,Hoffman GS,Hunder GG,Kallenberg CG. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 1994; 37:187-92.
2. Herbort CP, Cimino L, Ahmed M. Abu El Asrar AM: Ocular vasculitis: a mulitidisciplinary approach. Curr Opin Rheumatol. 2005; 17:25-33.
3. Deuter CME, Kotter I, Wallace GR, Murray PI, Stubiger N, Zirehut M. Behçet`s Disease: Ocular effect and treatment. Ret Eye Res 2008; 27:111-36.
4. Rhen T, Cidlowski JA. Antinflammatory action of glucocorticoids: new mechanism for old drugs. N Engl J Med 2005; 353:1711-23.
5. Mili-Boussen I, Letaief I, Zbiba W, Trabelsi O, Ben Younes N, Abid J, Azzabi S, Khalfallah N, Errais K, Ouertani A. Retinal vasculitis. Epidemiological, clinical and etiological features. J Fr Ophthalmol. 2010; 33:529-37.
6. Fraser-Bell S, Pavesio C. Advances in the treatment of intermediate and posterior uveitis. Exper Review of Ophtalmology 2008; 3:449-56.
7. Gangaputra S, Newcomb CW, Liesegang TL Kaçmaz RO, Jabs Da, Levy-Clarke GA, Nussemblat RB, Rosenbaum JT, Suhler EB, Thorne JE, Foster CS, Kempen JH. Methotrexate for ocular inflammatory diseases. Ophthalmology 2009; 116:2188-98.
8. Taylor SR, Habot-Wilner Z, Pacheco P, Lightman SL. Intraocular methotrexate in the treatment of uveitis and uveitic cystoid macular edema. Ophthalmology 2009; 116:797.
9. Lau CH, Comer M, Lightman S. Long-term efficasy of mycofenolate mofetil in the control of severe intraocular inflammation. Clin Experiment Ophthalmol 2005; 31:487–91.

10. Daniel E, Thorne JE, Newcomb CW, Pujari SS, Levy-Clarke GA, Nussemblat RB, Rosenbaum JT, Suhler EB, Foster CS, Jabs DA,Kempen JH. Mycophenolate mofetil for ocular inflammation. Am J Ophthalmol 2010; 149:423-32.
11. Kaçmaz RO, Kepmen JH, Newcomb C, Daniel E, Gangaputra S, Nussemblat RB, Rosenbaum JT, Suhler EB, Thorne JE, Jabs DA, Levy-Clarke GA, Foster CS. Cyclosporine for ocular inflammatory diseases. Ophthalmology. 2010; 117:576-84.
12. Kim EC, Foster CS. Immunomodulatory therapy for the treatment of ocular inflammatory disease: evidence based medicine recommendations for use. Int Ophtalmol Clin 2006; 113:1874-7.
13. Markomichelakis N, Delicha E, Masselos S, Fragiadaki K, Kaklamanis P, Sfikakis PP. A single infliximab infusion vs corticosteroids for acute panuveitis attacks in Behçet's disease: a comparative 4-week study. Rheumathology 2011; 50:593-7
14. Becker MD, Heiligenhaus A, Hudde T, Storsh-hagenlocher B, Wildemann B, Barisani-Asenbauer T, Thimm C, Stubiger N, Trieschmann M, Fiehn C. Interferon as a treatment for uveitis associated with multiple sclerosis. Br J Ophthalmol 2005; 89:1254-7.
15. Deuter CM, Koetter I, Guenaydin I, Stuebiger N, Zierhut M. Interferon alfa-2a: a new treatment option for long lasting refractory cystoid macular edema in uveitis. Retina 2006; 26:786-91.
16. Bodaghi B, Gendron G, Wechsler B, Terrada C, Cassoux N, Huong du LT, Lemaitre C, Fradeau C, LeHoang P, Piette JC. Efficacy of interferon alpha in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients. Br J Ophtalmol 2007; 91:335-9.
17. Myung JS, Aaker GD, Kiss S. Treatment of noninfectious posterior uveitis with dexamethason intravitreal implant. Clin Ophtalmol 2010; 4:1423-6.
18. Dada T, Dhawan M, Garg S, Nair S, Mandal S. Safety and efficacy of intraoperative intravitreal injection of triamcinolone acetonide injection after phacoemulsification in cases of uveitic cataract. J Cataract Refract Surg. 2007; 33:1613-8.
19. Choudhry S, Ghosh S. Intravitreal and posterior subtenon triamcinolone acetonide in idiopathic bilateral uveitic macular oedema. Clin Experiment Ophtalmol. 2007; 35:713-8.
20. Ishag M, Feroze AH, Shahid M, Biag AM, Ameen SS, Feroye SH, Chisti R. Intravitreal steroids may facilitate treatments of Eales` disease (idiopathic retinal vasculitis): an interventional case series. Eye 2007; 21:1403-5.
21. Suhler EB, Smith JR, Giles TR et al. Infliximab therapy for refractory uveitis: 2-year results of a prospective trial. Arch Ophthalmol 2009; 127:819.
22. Sfikakis PP, Theodossiadis PG, Katslari CG, Katsiari CG, Kaklamanis P, Markomichelakis NN. Effect of infliximab on sight-threatening panuveitis in Behçet's disease. Lancet 2001; 358:295.
23. Abu El-Asrar A, Al-Kharashi SA: Full panretinal photocoagulation and early vitrectomy improve prognosis of retinal vasculitis associated with tuberculoprotein hypersensitivity (Eale`s disease) Br J Ophtalmol 2002; 86:1248-51.
24. Stanford MR, David H. Diagnostic and therapeutic approach to patients with retinal vasculitis. Int Ophthalmol Clin 2000; 40:69-83.
25. Uveitis: How should we diagnose and treat our patients. / in conjunction with the American Uveitis Society. American Academy of Ophthalmology. Joint Meeting. Subspeciality Day Atlanta GA, 8. November, 2008
26. Nussenblatt RB, Whitcup SM, Uveitis: Fundamentals and Clinical Practice, Year book, Mosby, 2010, 229-235
27. Sobrin L, Kim EC, Christen W, Papadaki T, Letko E, Foster CS. Infliximab therapy for the treatment of refractory ocular inflammatory disease. Arch Ophthalmol 2007; 125:895-900.
28. Tugal-Tutkun I. Behçet's uveitis. Middle East Afr J Ophthalmol 2009; 16:219.
29. Elia T, Ben-Ari. Dual purpose: Some cancer therapies used to treat autoimmune disease. Journals Natl Cancer Inst 2004; 96:577-9.
30. Ebenezer D, Thorne JE, Newcomb CW, Pujari SS, Kaçmaz RO, Grace A, Levy-Clarke GA, Nussemblatt RB, Rosenbaum JT, Suhler EB, Foster SC, Jabs DA, Kempen JH. Mycophenolate Mofetil for ocular inflammation. Am J ophtalmol 2010; 149:423-32.
31. Yu EN, Meniconi ME, Tufail F, Baltatzis S, Foster CS. Outcomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis. Ocul Immunol Inflam 2005; 13:353-60.
32. Taylor SRJ, Salama AD, Pusey AD, Lightman S. Ocular manifestations of Wegener`s granulomatosis. Exp Review of Ophtalmol 2007; 2:91-103
33. Murphy CC, Greiner K, Plskova J. Cyclosporlne vs tacrolimus therapy for posterior and intermediate uveitis. Arch Ophthalmol 2005; 123:634.
34. Benitey-del-Castillo JM, Martiney de-la-casa JM, Pato-Cour, Mendey-Fernandey R, Lopey-Abad C, Matilla M, Garcia-Sanchey J. Long term treatment of refractory posterior uveitis with anti-TNFalpha (infliximab). Eye 2005; 19:841-5.
35. Kaburaki T, Araki F, Takamoto M, Okinaga K, Yoshida A, Numaga J, Fujino Y, Kawashima H. Best-corrected visual acuity and frequency of ocular attacks during the initial 10 years in patients with Behçet's disease. Graefe's Arch of Clin & Exp Ophthalmol 2010; 248:709-14

Efikasnost novih terapijskih modaliteta na izolovani okularni vaskulitis nasuprot okularnom vaskulitisu u sistemskoj bolesti

Gordana D. Zlatanović[1], Svetlana V. Jovanović[2], Maja Lj. Živković[1], Marko Lj. Zlatanović[1], Sunčica B. Srećković[2], Filip M. Radotić[3]

[1]Odeljenje retine, Očna klinika, Klinički centar Niš; [2]Odeljenje retine, Očna klinika, Klinički centar Kragujevac; [3]Medicinski fakultet, Univerzitet u Kragujevcu, Kragujevac; Srbija

SAŽETAK

Cilj Proceniti efikasnost novih terapijskih modaliteta u trogodišnjem periodu kod bolesnika s izolovanim vaskulitisom oka u poređenju sa vaskulitisom oka u sistemskoj bolesti.

Metode Efikasnost terapije procenjena je na osnovu promena u vidnoj oštrini i stepenu inflamacije oka (blaga, srednja, umerena, teška) i to sledećim parametrima: zamućenje staklastog tela, obloženost krvnih sudova, edem makule, okluzija krvnih sudova i neovaskularizacija.

Rezultati Novi terapijski modaliteti rezultuju smanjenjem broja bolesnika s teškom inflamacijom u grupi izolovanog vaskulitisa oka od 8 (13,5%) na 7 (12,2%), dok je procenat pacijenata s blagom inflamacijom povećan s 13 (20,7%) na 18 (29,3%) u istoj grupi ($p>0,05$). Procenat pacijenata s teškom inflamacijom u grupi okularni vaskulitis kao sistemska bolest, povećan je od 3 (16,2%) na 4 (21,6%). Ovo je uslovljeno prisutnošću bolesnika s Behçetovom bolesti u toj grupi. Procenat bolesnika s vidnom oštrinom ispod 0,1 smanjio se od 11 (17%) do 8 (13,4%) u grupi bolesnika okularni vaskulitis kao sistemska bolest, što je takođe uslovljeno brojem pacijenata s Behçetovim oboljenjem ($p>0,05$).

Zaključak Iako novi terapijski modaliteti nisu doveli do statistički značajnog poboljšanja vidne oštrine i smanjenja inflamacije, sistemska i intravitrealna kortikosteroidna terapija s imunomodulatornom terapijom predstavljaju efikasnu strategiju u formi izolovanog okularnog vaskulitisa i okularnog vaskulitisa kao dela sistemske bolesti.

Ključne riječi: vasculitis, biološki medikamenti, imunomodulatori

ORIGINAL ARTICLE

First sexual intercourse (sexarche) in youth in Bosnia and Herzegovina

Azra Hadžimehmedović[1], Adem Balić[2], Devleta Balić[3]

[1]Department of Gynecology and Obstetrics, University Clinical Center Tuzla, [2]Department of Gynecology and Obstetrics, Health Centre Tuzla, [3]Department for Human Reproduction "Dr Balić" ; Tuzla, Bosnia and Herzegovina

ABSTRACT

Aim To determine the average age of sexarche in young people in the territory of Bosnia and Herzegovina (B&H) in relation to their sex, place and life-style and religion.

Methods A survey (anonymous questionnaire) about sexual behavior of young people in the period 2007-2009 on the sample of 6000 individuals (experimental group of 5000 students and control group of 1000 non-students) has been conducted in four major university cities in B&H: Sarajevo, Tuzla, Mostar, Banja Luka.

Results A total of 3.659 (out of 6000, 61%) sexually active youth of which 1871 (51.1%) males, and 1788 (48.9%) females were observed. Among student population there were 3001 (82%), and among non-students 658 (18%) sexually active individuals. The mean (average) age of sexarche in sexually active youth as a whole was 17.34 (SD±1.77) in males and 18.20 (SD±1.84) in females ($p<0.001$), and among students and non-students, 17.72 (SD±1.81), and 17.92 (SD±2.04) ($p=0.02$), respectively ($p=0.01$). There was a significant difference of the average values of sexarche among members of different religions, in males ($p<0.001$) as well as in females ($p=0.004$) in both groups.

Conclusion Results of this study do not present a descending trend of the average age of first coitus in youth in BiH, which is contrary to the results of other countries.

Key words: youth, sexarche, sexual behaviour

Corresponding author:
Azra Hadžimehmedović
Department of Gynecology and Obstetrics
University Clinical Center Tuzla
Trnovac bb, 75000 Tuzla,
Bosnia and Herzegovina
Phone: +387 61 193 472;
fax: +387 35 311 210;
E-mail: azrahadzi@bih.net.ba

Original submission:
26 April 2011;
Revised submission:
12 July 2011;
Accepted:
03 August 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):74-78

INTRODUCTION

Sexarche is the first sexual intercourse in life. It is estimated that there is a significant increase in sexual activities among young people (20 years of age), as well as continuous descending trend of the average age of sexarche, which varies depending on sex, culture, living environment, race and socio-economic status (1,2).

Significant increase of sexual activity in young people, as well as decrease in the age of their first coitus, exposes them to risks of unplanned pregnancies and sexually transmitted diseases (3,4). Although humans develop sexuality through their entire life, for most people the first sexual intercourse is the key moment in that development (3). However, civilization, education, women emancipation, make the period between sexarche and pregnancy constantly prolonged (4).

Some authors emphasize that the changes in social context are the main reason youth begin with sexual activities at their earlier age. It is the consequence of availability of variety of public sources today comparing to previous years (5). Sexually explicit magazines, music videos and adverts which are full of sexual situations, movies that show scenes of sex, and rapid development of technology in the last 10 years, as well as general Internet presence all provide easy and cheap way of availability to porn pages, so that they have become a part of everyday life of young person (5).

According to literature the first sexual experience happens at the age of 15 in 39.9% female adolescents and 34.9% male adolescents in England, 47.1% male adolescents in Ukraine and 45.2% in Slovenia, and 38.5% female adolescents in Wales (6). On the other hand, only 17.2% of boys had sexual intercourse before the age of 15 in Spain and 2.7% in Macedonia (6).

The aim of this research was to determine the average age of sexarche in young people in the territory of Bosnia and Herzegovina in relation to sex, place and life-style and religion.

EXAMINEES AND METHODS

In the prospective study on the pattern of 6000 examinees of both sexes, aged 19 to 24, an anonymous poll on sexual behavior of youth in Bosnia and Herzegovina (Sarajevo, Tuzla, Mostar and Banja Luka) was conducted in period between 2007 and 2009.

In the experimental group 5000 students of both sexes were questioned; 1000 from each of five universities (University of Sarajevo, University of Tuzla, University of Banja Luka and two Universities of Mostar). The survey was conducted among students of different faculties, departments and academic years.

A control group consisted of 1000 young people of both sexes, aged 19 to 24, who were not students (250 non-students from each city: Sarajevo, Tuzla, Mostar and Banja Luka). Examinees were chosen randomly, with different places and way of living (with parents, on their own, in a dormitory), from different living and working environments, and different in religious and ethnic affiliation.

Questionnaires used in the prospective study consisted of 43 questions (26 were open-ended questions and 17 were with clearly defined response).

Approval for this study was given by referent B&H Universities.

Standard methods of descriptive and inference statistics were used, and quantitative data of sexarche were analysed with ANOVA statistical method. Qualitative data were tested by x^2 test and z test, which determined statistically significant difference of proportion. Level of significance $p<0.05$ was used in testing of statistical hypothesis.

RESULTS

There were 2508 (41.8%) males and 3492 (58.2%) females in the analyzed sample (Table 1). A total of 3.659 (out of 6000, 61%) sexually active youth of which 1871 (51.1%) males, and 1788 (48.9%) females (Table 2) were examined. Among student population there were 3001 (82%), and among non-students 658 (18%) sexually active individuals (Table 2).

The average age of sexarch in sexually active youth of both group analyzed was 17.34 (SD±1.77)

Table 1. Distribution of examined youth in B&H

	No of examines		
	Male (%)	Female (%)	Total (%)
Experimental group	2128 (35.5)	2872 (47.9)	5000 (83.4)
Control group	380 (6.3)	620 (10.3)	1000 (16.6)
Total	2508 (41.8)	3492 (58.2)	

Table 2. Distribution of examined youth in B&H in relation to their sexually activity

	No of sexual active individuals		
	Male (%)	Female (%)	Total (%)
Experimental group	1581 (43.2)	1420 (38.8)	3001 (82.0)
Control group	290 (7.9)	368 (10.1)	658 (18.0)
Total	1691 (51.1)	1788 (48.9)	

in males and 18.20 (SD± 1.84) in females (p<0,001). The average age of sexarche in the group of students was 17.72 (SD±1.81), 17.35 (SD±1.71) in males and 18.14 (SD± 1.83) in females, and in the group of non-students it was 17.92 (SD±2.04), 17.28 (SD±2.04) in males and 18.43 (SD±1.89) in females (p=0.02) (Table 3). The average age of sexarche in male students and non-students was 17.35 (SD±1.71) and 17.28 (SD± 2.04) (p=0.52), respectively, and in female students and non-students 18.14 (SD±1.83) and 18.43 (SD±1.89) (p=0,01), respectively (Table 3). In regard to religious affiliation, 1200 (20%) examinees were Orthodox, 2940 (49%) were Muslims, 1196 (19.9%) were Catholics, and 664 (11.1%) were members of other religions. There was a significant difference between the average value of sexarche according to different religious affiliations in the group of males (p<0.001), females (p=0.004) as well as between both sexes (p<0,001) (Table 4). In regard to the way of living 3042 (50.7%) of the examinees have been living with their parents, 2014 (33.6%) on their own and 944 (15.7%) live in a dormitory (Figure 1).

Table 3. The average age of sexarche of the experimental and control group in relation to gender

	Experimental group			Control group			T	p
	No of examinees	X	SD	No of examinees	X	SD		
Male	1851	17.35	1.71	290	17.28	2.04	0.64	0.52
Female	1420	18.14	1.83	368	18.43	1.89	-2.71	0.01
Total	3001	17.72*	1.81	658	17.92	2.04	-2.35	0.02

X, average age of sexarche,; SD, standard deviation; T, t-test;
*z=-2.35; p=0.01

Table 4. The average age of sexarche in examinees of both genders in relation to religious affiliation

Religion	Males		Females	
	M ± SD	p (F)	M ± SD	p (F)
Muslims	17.43±1.71*	p<0.001 (F 3,1867 =8,93)	18.43±1.88*	p<0.004 (F 3,1783 =4,54)
Catholics	17.60±1.77*		18.06±1.80*	
Orthodox	17.07±1.76*		18.12±1,79*	
Others	17.02±1.91*		18.07±1,90*	

M ± SD, age average value ± standard deviation;
*p<0,001

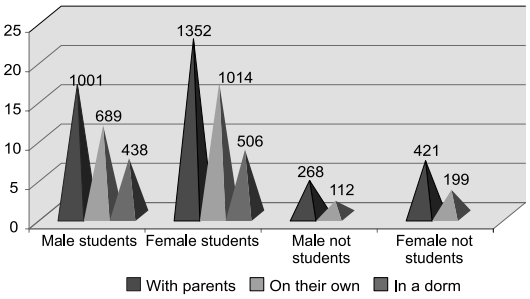


Figure 1. Distribution of examined youth in B&H in relation to sex and the way of living

DISCUSSION

It is generally accepted that the increase of sexual activity among young people resulted in shifting sexarche towards the younger age (7). Our data have shown that sexually active youth in B&H most commonly have their first sexual intercourse at the age of 17 and 18 for males and females, respectively. The average age of sexarche of both groups (experimental and control group) was significantly lower in males than in females, 17.34 18.20, respectively.

Previously conducted research among young people in secondary schools in Tuzla Canton has shown that sexarche occured in males at the age of 16 and in females at the age of 17 (7), which is slightly earlier in relation to the results of this study. The siituation is similar in the countries of our immediate surrounding (Croatia, Serbia, Slovenia), in which sexarche in males was between the age of 15 and 16, and in females between 16 and 17 (8-12). A project implemented in Serbia through questioning and research conducted in four cities has shown that sexarche was at the age between of 15.4 and 16.2 (13). According to UNICEF in the Federal Republic of Yugoslavia (Serbia and Montenegro), one third of girls and two thirds of boys had their first coitus before the age of 16 (14). Data from 2007 in Croatia has shown that 28.6% of boys and 16.5% of girls had their first sexual experience by the age of 16 (9).

Data about sexarche in other countries are different and in the range between 14 and19 years of age, boys get into their first sexual intercourse slightly earlier than girls (15-18). The proportion of female adolescents who had their first coitus before the age of 15 in the USA is 14%, in Canada, France, and Great Britain 4-9%, and in Sweden 12% (19). According to a research of Grunbaum et al., there were 45.6% of sexually active young persons in the USA, and 6.6% of these have reported they had the first coitus before the age of 13 (16). Between 40% and 50% of young people in countries like France, the Netherlands and Great Britain had sexual intercourse by the age of 18 (15).

According to the research of Gutmacher Institute from 2004, 77% of girls in Western countries had their first coitus before the age of 20, and 83% in sub-Saharan Africa and 56% in Latin America (20).

According to the report of HZJZ (Croatian In-

stitute for Public Health) 68% of male students were significantly sexually active ($p<0,001$) than 57% female students, and the average age of sexarche was 16.7 for males and 17.4 for females and students who were living on their own (males and females) were sexually more active than those who were living with parents. According to the results of this study sexual behavior of youth in B&H is similar to the neighboring countries.

Some authors in Croatia also refer to the shift of sexarche towards the younger age over time, stating that student population begins with sexual activities earlier (at the age of 17) compared to previous data with only 40% of students who had their sexual intercourse before the age of 18. The largest number of female students had their first coitus between the age of 18 and 20 (11). On the other hand, there are some data about relatively constant average age of sexarche (i.e. Swedish study 1999-2004), where the average age of sexarche was 17.6 in 1999 and 17.4 in 2004 (21). According to data about sexarche in students at the University of Tirana, sexarche among males was 17.9 and among females 18.8 years of age, which is similar to the results of this study (22). Later beginning of sexual activities in girls in our study is similar to some other world researches (23-25).

One of the studies conducted in the Balkans has shown that no religion (categorized into Muslims, Catholics, Orthodox and other) was independently associated with the age of sexarche (25). Our study has shown similar results.

In this research the average age of sexarche was significantly lower in students than in non-student population, which is contrary to the findings of some other authors stating that higher education delays the beginning of sexual activities (11, 24, 26).

Entering sexual relationships at early age mostly lead to some other forms of risky behavior. One of the studies done in the USA in 1988 has shown significant difference in sexual behavior between those who began their sexual activities before the age of 18 and those who began them later, e.g. the number of sexual partners was considerably higher in the group of examinees who began sexual activities at early ages (27).

The youth in B&H mostly begin their sexual relationships at the age of 17 and 18, males begin their sexual activities significantly earlier than females and young people with higher education enter sexual relationships earlier than their peers who are not students. It is important to emphasize that young people in Bosnia and Herzegovina begin sexual activities somewhat later than youth from neighboring countries.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Raine T, Minnis AM, Padian SN. Determinants of contraceptive method among young women at risk for unintended pregnancy and sexually transmitted infections. Contraception 2003; 68:19-25.
2. DeJong J, Jawad R, Mortagy I, Shepard B. The sexual and reproductive health of young people in the Arab Countries and Iran. Reproductive Health Matters 2005; 13:49-59.
3. Wellings K, Cleland J. Survays on sexual health: recent developments and future directions. Sex Transm Infect 2001; 77:238-41.
4. Jones R, Barton S. Introduction to hystory talking and principles of sexual health. Postgrad Med J 2004; 80:444-6.
5. Štulhofer A. Sociocultural and psycho-social aspects of risk sexual behavior. Medicus 2009; 18 (suppl 1):123-9.
6. Chapman JR. Adolescent sex and mass media: a developmental approach. Adolescence Winter 2000; 140:799-811.
7. Hadžimehmedović A, Balić A, Balić D. Sexual behaviour of adolescents in Tuzla Cantone. Gynaecol Perinatol 2006; 15(suppl 3):142-8.
8. Hodžić A, Bjelić N. Significance of gender in attitudes and sexual behavior of adolescents. Research report: Men, Women and Sexuality. Zagreb: CESI, 2003:1-182.
9. Kuzman M, Pavić Šimetin I, Pejnović Franelić I. Early sexual intercourse and risk factors in Croatian adolescents. Coll Anropol 2007; 31(suppl 2):121-30.
10. Klavs I, Rodrigues CL, Weiss HA and Hayes R. Factors associated with early sexual deut in Slovenia: results of a general population survey. Sex Transm Infect 2006; 82:478-83.
11. Čorkalo D, Renić D. Attitudes, knowledge and behaviour of students in relation to AIDS. Social Research Zagreb 1998; 2-3:287-304.
12. Kapamadžija A, Bjelica A, Segecdi D. Sex knowledge and behavior in male high school students. Med Pregl 2000; 53:595-9.

13. RAR. Rapid assessment and response on HIV/AIDS among especially vulnerabile young people in Serbia. Beograd: UNICEF 2002: 44-6.
14. UNICEF. Young People in Changing Societies. Regional Monitoring Reports, No.7. Florence. Siena-Italy: UNICEF Innocenti Research Centre 2000:29-35.
15. WHO. Regional Strategy on sexual and Reproductive health 2001. Entre nous: The European Magazine for sexual and reproductive health No.50-2001. Copenhagen-Denmark; WHO, 2001.
16. Grunbaum JA, Kann L, Kinchen SA, Williams B, Ross JG, Lowry R, Kolbe L. Youth risk behavior surveillance–United States, 2001. MMWR Surveill Summ 2002; 51(SS-4):1-62.
17. Auslander BA, Rosenthal SL, Fatenberry D, Biro FM, Bernstein DI, Zimet GD. Predictors of sexual satisfaction in an adolescent and college population. J Pediatr Adolesc Gynecol 2007; 20:25-8.
18. Virtala AM, Kunttu K, Huttunen A, Virjo IO. Sexual intercourse and current contraceptive use among university students in Finland. Eur J Obstet Gynecol Reprod Biol 2007; 135(suppl 1):104-10.
19. Darroch JE, Singh S, Frost J and Study team. Differences in Teenage Pregnancy Rates Among Five Developed Countries: The Roles of Sexual Activity and Contraceptive use. Fam Plan Perspectives 2001; 33:244-50.
20. The Alan Guttmacher Instutute . Facts in brief. Induced abortion worldwide. New York, The Alan Gutmacher Institute, 2004.
21. Larsson M, Tyden T. Increased sexual risk taking behaviors among Swedish female university students: repeated cross-sectional surveys. Acta Obstet Gynaecol Scand 2006; 85:966-70.
22. Burazeri G, Roshi E, Tavanxhi N, Orhani Z, Malo A. Sexual Practices of Undergraduate Students in Tirana, Albania. Croat Med J 2003; 44 (suppl 1): 80-5.
23. Singh S, Wulf D, Samara R, Cuca YP. Gender Differences in the Timing of First Intercourse: Data from 14 Countries. Int Fam Plan Perspectives 2000; 26 (suppl 1): 21-8.
24. Hansen L, Mann J, McMahon S, Wong T. Sexual Health. BMC Womens Health 2004; 4 (suppl 1):S24-8.
25. Delva W, Wuillaume F, Vansteelandt S, Claeys P, Verstraelen H. Sexual behaviour and contraceptive use among youth in the Balkans. Eur J Contracept Reprod Health Care 2007; 12 (suppl 4):309-15.
26. Petrović J, Mihić I, Zotović M. Forms and frequency of risky behaviour in female students at the University of Novi Sad. Pedagoška stvarnost 2007; 53:875-91.
27. Yarber W, Parillo. Adolescents and Sexually Transmitted Diseases. J Sch Health 1992; 62 (suppl 7):331-8.

Prvi spolni odnos (seksarha) kod omladine u Bosni i Hercegovini

Azra Hadžimehmedović[1], Adem Balić[2], Devleta Balić[3]

[1]Ginekološko-akušerska klinika, Univerzitetski klinički centar Tuzla; [2]Služba za ginekologiju i perinatologiju, Dom zdravlja Tuzla; [3]Zavod za humanu reprodukciju "Dr. Balić"; Tuzla, Bosna i Hercegovina

SAŽETAK

Cilj Odrediti srednju dob seksarhe kod omladine oba spola, na području Bosne i Hercegovine, u odnosu na spol, mjesto i način stanovanja, te u odnosu na vjeroispovijest.

Metode U periodu od 2007. do 2009. godine na području BiH provedeno je ispitivanje (anonimna anketa) o spolnom ponašanju omladine na uzorku od 6.000 ispitanika (eksperimentalna grupa od 5.000 studenata i kontrolna grupa od 1.000 mladih ljudi koji nisu studenti). Istraživanje je provedeno u četiri najveća univerzitetska grada (Sarajevo, Tuzla, Mostar i Banja Luka).

Rezultati Spolno aktivnih mladih ljudi bilo je ukupno 3.659 (61% od 6.000 ispitanika), od čega mladića 1.871 (51,1%), djevojaka 1.788 (48,9%), te studentske omladine 3.001 (82%) i nestudentske omladine 658 (18%). Srednja dob seksarhe kod spolno aktivne omladine u BiH je iznosila 17,34 godine (SD±1.77) kod muškog i 18,20 godine (SD±1.84) kod ženskog spola. Srednja dob seksarhe u sveukupnoj studentskoj populaciji iznosila je 17,72 godina (SD±1.81), a kod onih koji nisu studirali 17,92 godina (SD±2.04), te je bila značajno manja u ženskoj populaciji između ove dvije grupe (p=0,01). Ustanovljena je značajna razlika srednjih vrijednosti seksarhe između pripadnika različitih vjeroispovijesti, kako muških (p<0,001), tako i ženskih (p=0,004), u obje ispitivane grupe. Srednja dob seksarhe je statistički značajno (p<0,001) bila manja kod muškaraca, nego kod žena, u obje ispitivane grupe, te kod eksperimentalne u odnosu na kontrolnu grupu (p=0,02).

Zaključak Suprotno našim očekivanjima kod mladih ljudi u Bosni i Hercegovini nije zabilježen trend pomjeranja dobne granice prema mlađoj dobi pri prvom spolnom odnosu, što je u suprotnosti s rezultatima iz drugih zemalja.

Ključne riječi: omladina, seksarha, spolno ponašanje

ORIGINAL ARTICLE

Epidemiological, clinical and pathological characteristics of colorectal cancer in patients treated at the Clinical Center of Tuzla University

Jasmina Alidžanović[1], Nada Pavlović[2], Nermin Salkić[2], Enver Zerem[2], Amra Čičkušić[3]

[1]Department of Oncology, Clinic of Oncology, Haematology and Radiotherapy; [2]Department of Gastroenterology, Clinic of Internal Medicine; [3]Department of Nuclear Medicine, Clinic of Radiology; Clinical Center of Tuzla University, Bosnia and Herzegovinia

ABSTRACT

Aim To investigate hospital morbidity and incidence of colorectal cancer (CRC) in the Tuzla Canton between 2000 and 2004, as well as mortality incidence and degree of disease progression.

Methods A total of 383 patients were enrolled in this study, all of them with CRC. Pathohistological analyses were performed in all patients after colonoscopy. Afterwards, the patients underwent surgery and obtained material was also pathohistologically analyzed in order to perform the Astler-Coller classification and the classification of the location of CRC.

Results In the period 2000-2004 in the Tuzla Canton there were 383 newly diagnosed patients with CRC. The average age of the patients was 62±12 years, and the incidence was equally distributed per genders. Rectal tumour was noted in 145 (37.9%) patients, and in 238 (62.1%) tumor was found elsewhere in the colon. Average incidence of the CRC was 15.73/100,000, with a dramatic increase in incidence in 2003 of 27.40/100,000. The average mortality incidence during the study was 6.89/100,000, and the largest number of the patients (339, 88.6%) was in an advanced stage of the disease.

Conclusion There has been a significant increase in the number of newly detected cases of CRC in the Tuzla Canton during 2000-2004, which implies the need for initiating a National Early CRC Detection Programme.

Keywords: colorectal cancer, epidemiology, incidence

Corresponding author:
Jasmina Alidžanović
Department of Oncology,
Clinical Center of Tuzla University
Trnovac bb, 75 000 Tuzla,
Bosnia and Herzegovina
Phone: +387 61 73 19 70;
fax: +387 35 25 25 22;
E-mail: alidzanovic_jasmina@hotmail.com

Original submission:
27 August 2011;
Revised submission:
03 October 2011;
Accepted:
18 October 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):79-85

INTRODUCTION

Colorectal cancer (CRC) represents the most common malignant tumor of the gastrointestinal tract, it is the third most common malignant disease, and the second most common cause of death in both genders (1). It has been reported that the disease frequency correlates with the industrial development of certain countries (2). The highest incidence rates were registered in the USA, where 145,000 new cases are diagnosed and 55,000 patients die as a consequence every year (3). Low incidence rates are found in Africa, Asia and some regions of South America (4). Western Europe and Scandinavia have middle incidence rates, while the East-European countries have low incidence rates (5). The incidence of the CRC is growing in most countries of the world, however the mortality in the western Europe and North America is decreasing, probably due to early detection and diagnosis, as well as more successful treatment (6). Analysis of the population which encompasses the activities of the National Institute for Cancer Observation, epidemiology and the final results show that the changes in the use of the endoscopic polypectomy, calories intake, physical activities, serum cholesterol, reduced smoking as well as obesity, have all caused the incidence to fall after 1986 (1).

In the European Union in 2000, CRC was the most frequent of all malign diseases, with a total of approximately 258,000 patients, 123,000 of which were male and 135,000 female. 138,000 patients died in the same year, 70,000 males and 68,000 females (7).

According to the data from the Cancer Registry of the Croatian National Institute of Public Health, CRC is the second most common cancer form in men and women, second to lung and breast cancer, respectively, with prevalence of 15% in males, and 13% in females, in relation to the total number of all diagnosed malign diseases. The alarming data depicting the rise in the number of the new cases of CRC in Croatia (1983 – 2004 from 1,186 to 2653 cases, i.e. 124%) – has led to a development of a National Early CRC Detection Program in Croatia (8).

Bosnia and Herzegovina does not possess a national malign neoplasm registry, which is the reason for nonexistence of any CRC incidence data in our country (9). In the Tuzla Canton - according to the data of the Public Health Institute in Tuzla there was a CRC incidence of 13.8/100,000 (10).

The aim of this study was to analyze the morbidity, the cumulative incidence and mortality and the disease progression degree of colorectal cancer in the Clinical Center of Tuzla University, in a five-year period (2000 - 2004).

PATIENTS AND METHODS

Patients

The patients were mainly hospitalized at the Departments of Internal Medicine and Surgery, but also at the Clinic for Infectious Diseases of the Clinical Center of Tuzla University. There were also patients who were treated in outpatient clinics. Patients who were hospitalized at the Department of Internal Medicine, underwent colonoscopy with biopsy, while the pathohistological analyses were performed at the Clinic for Pathology and Laboratory Diagnostics of the Clinical Center of Tuzla University. Thereafter, they underwent surgery at the Department of Surgery of the Clinical Center of Tuzla University, and the pathohistological analyses were performed at the Clinic for Pathology of the Clinical Center of Tuzla University. In a few urgent cases, patients were hospitalized in the Department of Surgery and underwent surgery without previous diagnostic treatment. The Tuzla Canton population, approximately 600,000 people, is mainly concentrated in the vicinity of the Clinical Center of Tuzla University.

Methods

The pathohistological material were obtained from 383 patients and analyzed in order to perform the Astler-Coller classification and the classification of the location of CRC (11). The classification of locations was the following: 1. rectum, 2. sigmoid colon, 3. descending colon, 4. transverse colon, 5. ascending colon and 6. caecum. A total number of the CRC in each location was determined, as well as the percentage of each localization in correlation with the total number of CRC in five years. Furthermore, a number of the CRC classified by Astler-Coller classification (A, B1, B2, C1, C2 and D) was determined, in absolute values for each year in

the 5–year period including a percentage of each stage in comparison to the total number.

The TNM (Tumor Nodus Metastasis) classification was performed before the operative treatment, based on physical examination, and other clinical diagnostic methods, giving a prefix ''c'' to a ''TNM'' mark meaning that the mentioned categories were processed clinically (12). Afterwards, the clinical classification was updated with the new data, especially those received after the pathohistological examination of the surgically obtained tissue. In that case, the ''TNM'' mark changes received a prefix ''p'' meaning that the categories were confirmed with a pathohistological examination.

The main criteria for dividing tumor into categories was its anatomical distribution, which depends on the three characteristics: the size of the tumor and its areal and depth distribution, cancer expansion to regional lymph nodes, and existence of distant metastases. All of these parameters can be found in the final PHD report according to Astler-Collers classification (11).

Statistical methods

A computer database has been designed, containing all necessary data for statistical analysis, which was performed using the SPSS 15.0 software package (SPSS Inc., Chicago, USA). The basic descriptive statistics' tests were used for all variables. The T-tests were performed for determining the differences between the quantitative variables, while the qualitative variables' differences were tested using X^2-tests with the continuity correction for 2x2-tables.

RESULTS

In the observed 5-year period (2000-2004), 383 new cases of CRC were detected, 238 (62.1%) of which were located in colon and 145 (37.9%) in rectum (Table 1).

Males and females were represented with 195 (49.9%) and 192 (50.1%) patients (Figure 1).

Table 1. Distribution of new cases of colon and rectum cancer during 2000-2004 period

Localization	Number of diagnosed CRCs per year				
	2000	2001	2002	2003	2004
Colon	46	47	44	71	39
Rectum	23	29	17	43	24
Total	69	76	61	114	63

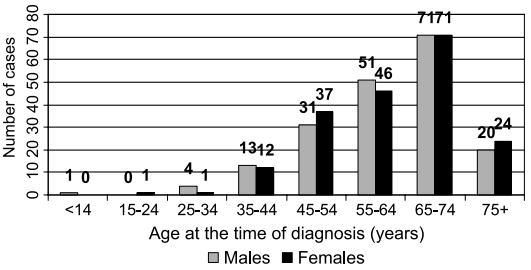


Figure 1. Frequency of colorectal carcinoma according to sex and age

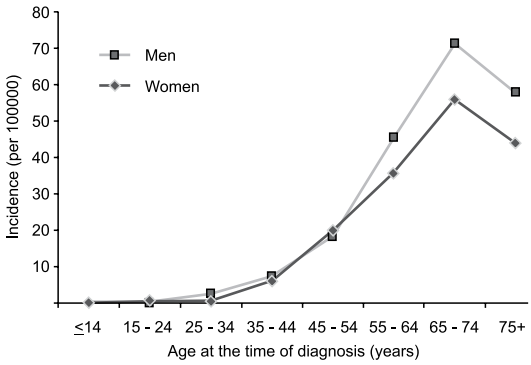


Figure 2. Description of incidence change according to sex and groups

Rectal cancer as a primary location occurred in 145 (38%) patients, and 238 (62%) patients had the primary location in other parts of the colon, 102 (26.6%) had the CRC in the ascending colon, 119 (31%) in the descending and 17 (4.4%) patients in the transversal part of colon.

The average incidence of CRC was 15.43/100,000 (%95 CI = 13.89 - 16.98), 15.73/100,000 in males and 15.15/100,000 in females (Figure 2).

Incidence standardized by age for all probands (according to standard European population) was 14.69/100,000 (%95 CI = 11,79 - 17,58) (Figure 3).

The average mortality incidence for the period 2000-2004 was 6.89/100,000 (%95 CI = 5.86 – 7.92), in males 6.42/100,000 and in females

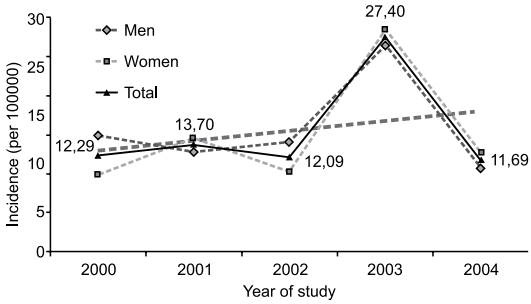


Figure 3. Description of incidence changes and trend according to sex and the year of follow up (the numbers apply to the overall incidence; dashed line represents the trend line)

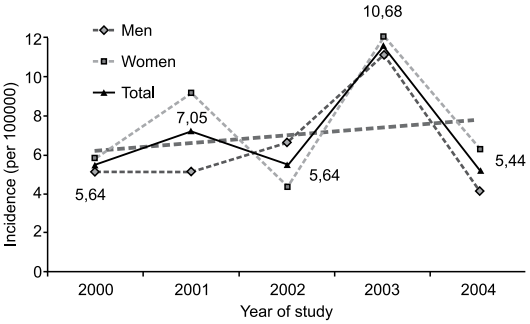


Figure 4. Description of mortality incidence ratio and trend according to sex and the year of follow up (the numbers on this graph apply to the overall incidence; dashed line represents the trend line)

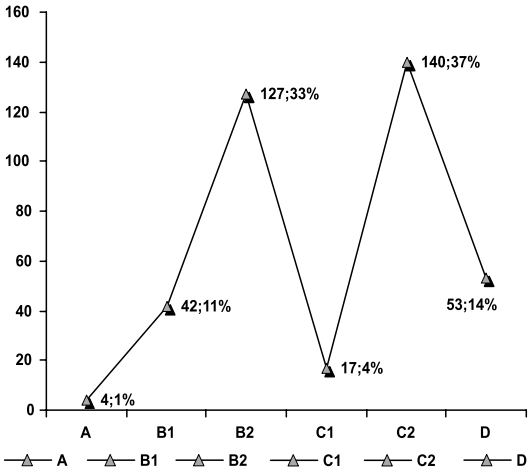


Figure 5. Percentage of individual stages according to Astler-Coller-s classification

7.34/100,000. Mortality standardized by age for the total population was 6.55/100,000 (%95 CI = 5.26 – 7.84) (Figure 4).

Based on this data, cumulative and standardized morbidity and mortality incidence of the probands have been determined considering the primary tumor location (rectum or colon) (Table 2). Morbidity and mortality incidence of colon location is higher than for rectum location (9.59 vs. 5.84, and 4.35 vs. 2.54, respectively).

Regarding the disease progression degree, 46 (out of 383, 11.4%) patients had an early stage of CRC, while 337 (88.6%) patients had the advanced stage of the disease. Distribution of certain CRC stages according to the depth of the colon wall invasion, according to Astler-Coller classification is shown in 5 Figure 5. Stages B2 and C2 were diagnosed in 70% of cases and 14% of the patients with stages C1 and D.

DISCUSSION

The CRC incidence in the Tuzla Canton has been growing from 12.29 to 27.4/100.000 in the period 2000–2004, with the average incidence of 15.43/100.000, and matches the CRC incidence growth in the neighboring countries, as well as in the European countries and the rest of the world (13). According to the data of the Croatian Cancer Registry, the total CRC incidence in 2005 was 63.8/100.000 (14). Unfortunately, Bosnia and Herzegovina does not have a National Cancer Registry and consequently, information on the total number of CRC patients or the incidence of this disease (9). In the European Union approximately 259.000 new cases of CRC have been reported in 2000 (7). The yearly CRC incidence worldwide is rising and it is currently up to 60/100.000 (7).

The age analysis of the probands has shown that most CRC patients were in the fifth, sixth or the seventh decade, with the average age of 62±12 at the time of the disease detection. This confirms the theory that old age is one of the CRC risk factors, which is also influenced by the fact that modern societies with both the higher life standards and more developed health care have an increase of the older population, which has ultimately led to the greater presence of CRC (15). In the USA, as well as in the developed European countries, CRC presents itself mostly in the 65th year (16). The data of the Croatian National Institute of Public Health have shown that in 2005 there was a larger number of males affected by CRC than females (6). In this study the gender analysis of probands has shown almost equal presence of

Table 2. Symple et standard incidence of hospital morbidity and mortality of site specific colorectal carcinoma

Localization	Morbidity		Mortality	
	Symple incidence (CI)	Standard incidence (CI)	Symple incidence (CI)	Standard incidence (CI)
Colon	9,59/105 (%95CI=8,03-11,15)	9,15/105 (%95CI=7,34-10,95)	4,35/105 (%95CI=3,53-5,17)	4,18/105 (%95 CI=3,34-5,01)
Rectum	5,84/105 (%95CI=5,10-6,58)	5,54/105 (%95CI=4,45-6,63)	2,54/105 (%95CI=1,91-3,17)	2,38/105 (%95CI=1,92-2,84)

CRC in both males and females, and most males were in the age between 55 and 65 years, but the incidence was higher in males than females due to a higher number of female population in the Tuzla Canton. In developing countries these rates are substantially higher in males than in females (17). Such unfavorable trends are considered to reflect a combination of factors including changes in dietary patterns, obesity, and increased prevalence of smoking (18,19).

Regarding the location of CRC, our results have shown that the disease more frequently affected various regions of the colon as opposed to the rectum, with a significant portion bound to the descending and sigmoid colon. A Chinese study suggests no distal-to-proximal shift of colorectal adenoma and CRC among the Chinese population in Shanghai over the past 12 years, which is different from the data from Western parts of the world with more colorectal lesions located in the distal part (20).

According to the data of the (American) National Cancer Institute, the CRC incidence in the caecum and the ascending colon has risen from 33.9% to 36.1%, and the incidence in the transversal and the descending colon from 15.8% to 17.2% (21). It has been assumed that the cause for such figures is the improved diagnostics, i.e. the application of the complete colonoscopy instead of the earlier most commonly applied rigid rectoscopy (22).

Based on the data obtained in this study the CRC mortality has shown increasing trend during the 2000-2004 period. The group of patients affected by the colon cancer has presented significantly higher simple and standardized morbidity and mortality incidences in this study compared to these rates in patients affected by the rectum cancer, and both were lower than in other countries. This is most probably caused by a lower degree of health education in Bosnia and Herzegovina compared to other countries, inexistence of a National Early CRC Detection Program or the National Cancer Registry, and irregular reporting of malign diseases. According to the results of pathohistological Astler-Coller classification there a was significantly higher number of patients with the advanced stage of CRC than those with an early phase of the disease. The German study showed that young age was a risk factor for aggressive CRC, according to stage of the disease (23). All tumor characteristics, particularly T, were worse for colon as compared to rectal tumors (23).

Such a large number of patients in our study presented with the advanced and metastatic CRC (Astler-Coller C1-D) was probably a consequence of the underdeveloped primary and secondary disease prevention, as well as of the inexistence of the National CRC Detection Program. Most patients seek medical attention upon the appearance of the symptoms, which are unfortunately signs of an advanced stage of the disease (24).

In conclusion, there has been a significant rise in the number of newly detected cases of CRC in the Tuzla Canton between 2000 and 2004, the disease started presenting itself at the age of 40, with strong rise around the age of 55, and most people were affected during the 7th decade. The number of the patients with the advanced stage of CRC was significantly larger than the number of the patients with an early stage of the disease, which implies the need to initiate a National Early CRC Detection Program.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Murphy Tk, Calle EE, Rodriguez C, Kahlinn HS, Thun MJ. Index and Colon cancer mortality in a large prospective study. Am Epidemiol 2000; 152:847-54.
2. Sarli L, Michiara M, Sqarqi P, Iusco D, De Lisi V, Leonardi F. The changing distribution and survival of colorectal carcinoma: an epidemiological study in an area of northern Italy. Eur J Gastroenterol Hepatol 2005; 17:567-72.
3. Jemal A, Siegel R, Warol E, Hao Y, Xu J, Thum M. Cancer statistics 2009. Ca Cancer J Clin 2009; 59:225-49.
4. Center MM, Jemal A, Warol E. International trends in colorectal cancer incindence rates. Cancer Epidemiol Biomarkers Prev 2009; 18:1688-94.
5. Cancer Data base. Report on The American Gastroenterological Association. Preventing colorectal cancer colorectal cancer: A Clinician Guide. Can-

cer incidence in five continents. Iarc Sci Publ 2005; 1997:1-1240.
6. Ferly J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007; 18:581-92.
7. Ponz de Leon M, Marino M, Benatti P, Rossi G, Menigatti M, Pedroni M Di Gregorio C, Losi L, Borghi F, Scarselli A, Ponti G, Roncari B, Zangardi G, Abbati G, Ascari E, Roncucci L. Trend of incidence, subsite distribution and staging of colorectal neoplasms in the 15-year experience of a specialised cancer registry. Ann Oncol 2004; 15:940-6.
8. Incidencija raka u Hrvatskoj 1980-2000, Bilten br 27. Zagreb: Hrvatski zavod za javno zdravstvo, 2002.
9. Ferković V. Registar malignih neoplazmi Tuzlanskog kantona, 2001/2002. Tuzla: Univerzitet u Tuzli, 2004.
10. Ferković V, Mehinović N. Registar malignih neoplazmi na području Tuzlanskog kantona. The register of malign neoplasm in the area of the Tuzla Canton. In: Abstracts of papers, First B&H Congress of Occupational Medicine, 22-25th May 2003, Tuzla, Bosnia and Herzegovina. University of Tuzla, , Tuzla 2003; 42-46.
11. American Joint Committee on Cancer. Colon and rectum. In: AJCC Cancer Staging Manual. 6th ed. New York, NY: Springer, 2002: :113-24.
12. Edge BB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging moment and the future of TNM. Ann Surg Oncol 2010; 17:1471-4.
13. Sarli L, Michiara M, Sgargi P, Iusco D, De Lisi V, Leonardi F, Bella MA, Sgobba G, Roncoroni L. The changing distribution and survival of colorectal carcinoma: an epidemiological study in an area of northen Italy. Eur J Gastroenterol Hepatol 2005; 17:567-72.
14. Incidencija raka u Hrvatskoj 2005, Bilten br 30. Zagreb: Hrvatski zavod za javno zdravstvo.
15. Murphy Tk, Calle EE, Rodriguez C, Kahlinn HS, Thun MJ. Index and colon cancer mortality in a large prospective study. Am Epidemiol 2000; 152: 847-54.
16. Marti-Rague J, Pares D, Biondo S, Navarro M, Figueras J, de Oca J, Pareja L, Cambray M, del Río C, Osorio A, Novell V, Jaurrieta E. Survival and recurrence in the multidisciplinary approach of colorectal cancer. Med Clin 11 2004; 123:291-6.
17. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. Ca Cancer J Clin 2011; 61:69-90.
18. Center MM, Jemal A, Smith RA, Ward E. Worldwide variations in colorectal cancer. CA Cancer J Clin 2009;; 59:366-78.
19. de Kok IM, Wong CS, Chia KS. Gender differences in the trend of colorectal cancer incidence in singapore, 1968-2002. Int J Colorectal Dis 2008; 23:461-7.
20. Bai Y, Gao J, Zou DW, Li ZS. Distribution trends of colorectal adenoma and cancer: a colonoscopy database analysis of 11,025 Chinese patients. J Gastroenterol Hepatol 2010; 25:1668-73.
21. Howlader N, Noone AM, Krapcho M, Neyman N, Aminou R, Waldron W, Altekruse SF, Kosary CL, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Eisner MP, Lewis DR, Chen HS, Feuer EJ, Cronin KA, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2008, Bethesda: National Cancer Institute. http://seer.cancer.gov/csr/1975_2008/ (2th October, 2011).
22. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: A population-based study. *J Nati Cancer Inst* 2003; 95:230–6.
23. Hemminki K, Santi I, Weires M, Thomsen H, Sundquist J, Bermejo JL. Tumor location and patient characteristics of colon and rectal adenocarcinomas in relation to survival and TNM classes. BMC Cancer 2010; 10:688.
24. Šamija M, Vrdoljak E, Krajina Z, eds. Clinical Oncology. 1. ed. Zagreb: Medicinska Naklada, 2006: 211-31.

Epidemiološke, kliničke i patološke karakteristike kolorektalnog karcinoma u pacijenata liječenih u Univerzitetskom kliničkom centru Tuzla

Jasmina Alidžanović[1], Nada Pavlović[2], Nermin Salkić[2], Enver Zerem[2], Amra Čičkušić[3]

[1]Odjel za onkologiju Klinike za onkologiju, hematologiju i radioterapiju, [2]Odjel za gastroenterologiju Klinike za interne bolesti, [3]Odjel za nuklearnu medicinu Klinike za radiologiju; Univerzitetski klinički centar Tuzla, Bosna i Hercegovina

SAŽETAK

Cilj Istražiti morbiditet i incidenciju kolorektalnog karcinoma na području Tuzlanskog kantona, u periodu od 2000. do 2004. godine, te incidenciju mortaliteta i stepen uznapredovalosti bolesti.

Metode U studiju su bila uključena 383 pacijenta kod kojih je potvrđena dijagnoza kolorektalnog karcinoma. Kod svih pacijenata urađena je kolonoskopija s ciljanom biopsijom, a patohistološke analize su rađene na Klinici za patologiju i laboratorijsku dijagnostiku. Pacijenti su operisani u hirurškoj Klinici i

operativni materijal je takođe patohistološki analiziran na Klinici za patologiju. U dobijenom materijalu izvršena je klasifikacija kolorektalnog karcinoma po Astler-Collerovoj patohistološkoj klasifikaciji i regionalnoj distribuciji.

Rezultati Na području Tuzlanskog kantona, u periodu od 2000. pa do kraja 2004. godine, registrirana su 383 novodijagnosticirana kolorektalna karcinoma. Prosječna dob oboljelih pacijenata iznosila je 62±12, s podjednakom zastupljenošću muških i ženskih ispitanika. Rektalna lokalizacija je zabilježena kod 145 (37,9%), a lokalizacija u drugim dijelovima kolona kod 238 (62,1%) ispitanika. Prosječna incidencija kolorektalnog karcinoma iznosila je 15,73/100.000, a daleko najviša incidencija zabilježena je u 2003. godini, 27,40/100.000 stanovnika. Prosječni mortalitet iznosio je 6,89/100.000 stanovnika. Najveći broj ispitanika bio je u uznapredovalom stadiju bolesti, odnosno 339 (88,6%) pacijenata.

Zaključak Zabilježen je značajan porast broja novootkrivenih pacijenata oboljelih od kolorektalnog karcinoma u periodu od 2000. do 2004. godine, što implicira potrebu za formiranjem nacionalnog programa za rano otkrivanje i prevenciju kolorektalnog karcinoma.

Ključne riječi: kolorektalni karcinom, epidemiologija, incidenca

Obesity and related factors in 7-12 year-old elementary school students during 2009-2010 in Sari, Iran

Salar Behzadnia[1], Koorosh Vahidshahi[1], Seyyed Hamzeh Hosseini[2], Shideh Anvari[3], Sara Ehteshami[2]

[1]Mazandaran University of Medical Sciences Department of Pediatrics, [2]Mazandaran University of Medical Sciences Department of Psychiatry,[3]Education Development Center, Mazandaran University of Medical Sciences

ABSTRACT

Aim To define the prevalence of obesity and its related factors in 2-7 year-old elementary school students in Sari city (Mazandaran, Iran).

Methods In this descriptive cross sectional study, which was conducted in the 2009-2010 period**,** the study population included 7-12 year-old first to fifth grade elementary school students in Sari. Sampling was multi-stage and stratified randomization at level of the target students. Student's height and weight were measured using stediometer and digital scales. Body Mass Index (BMI) was calculated. A questionnaire about feeding habits and socio-economic status(SES) of families was used. Data collection was performed using phone interview with parents also the questionnaire's records. Analysis was done in SPSS16 using appropriate statistical tests, $p<0.05$ was considered as significant.

Results Of 653 students, 297 (45.5%) were male, 177 (27.4%) children were overweight (BMI>85%) and 78 (12%) were obese (BMI> 95%). Higher prevalence of obesity in the children with good socio economic status was found (p=0.001). Significant relationship between usage of fast food and obesity, and between school grade and obesity (p= 0.001) was found.

Conclusion The overall prevalence of obesity in studied children was high, which suggests the need for serious attention in the health system, extensive studies, also designing and implementation of interventions with regard to childhood obesity.

Key words: obesity, related factors, elementary students

Corresponding author:
Sara Ehteshami
Educatin Development Center, Mazandaran University of Medical Sciences
Valie asr Blv, Sari, Mazandaran, Iran
Phone: +981 51 214 4328.;
fax.: +981 51 227 3689;
Email: Sara_eh59@yahoo.com

Original submission:
27 July 2011;
Revised submission:
29 August 2011;
Accepted:
28 October 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):86-90

INTRODUCTION

Obesity is a metabolic disorder that is characterized by increased body fat (1). Different criteria are considered for the diagnosis of obesity, but the most common criterion in studies is using the BMI (Body Mass Index). On this basis, 85% <BMI <95% is defined as overweight, BMI> 95% as obese and BMI> 99% as severely obese. Obesity and overweight in children is one of the recently considered issues in health literature. According to the National Center for Health and Nutrition of America, 18.8% of 6-11 year-old American children (up to 30% in some races) are overweight (2). According to studies during the years 2003-2004 in our country, the prevalence of overweight and obesity in school children in 23 provinces capitals was 9.8% and 4.4% respectively (3,4), also based on studies in the year 2007, the prevalence of obesity in Mazandaran province was 4.2% (5).

Childhood obesity leads to serious complications in both childhood and adulthood periods, some of them include: psychological-social problems, growth disorders early menarche, cardiovascular problems, metabolic problems (insulin resistance, elevated cholesterol, etc.), orthopedic problems, respiratory problems, and nervous system problems during the childhood, also a promoting factor for obesity and related problems in adulthood. These complications are associated with the severity of obesity therefore can be usually reduced or completely removed by weight loss (4).

Timely detection of risk factors, also high risk children for overweight are critical for appropriate effective interventions in initial phase of obesity. According to special importance of pediatric obesity also the role of genetic, lifestyle and environmental factors as risk factors of obesity, and considering the lack of a comprehensive study on this issue in our area, in this research the prevalence of obesity and its related factors in 2-7 year-old elementary school students in Sari city was studied in the school years 2009-2010 (5).

The aim of this study was to define the prevalence of obesity and its related factors in 2-7 year-old elementary school students in Sari city (Mazandaran, Iran) .

The study would be the first step in designing of intervention for preventing childhood obesity.

EXAMINEES AND METHODS

The descriptive cross sectional population study included 7-12 year-old first to fifth grade elementary students in Sari in 2009-2010. The sample size was determined to be 650 students.

Sampling was multi-stage (clustering at level of the schools), and stratified randomization at the level of the students.

Each student's height without shoes in straight standing style and when the heels of the foot, back of hips and head was stuck to the wall was measured using stediometer (KWS Medical Supplies, LLC, USA) with movable ruler and a 0.1 centimeter precision.

Weight was measured with minimum clothing, without shoes, using digital scales (Burer, Germany) and 0.1 kg precision. The average of the three measurements was considered.

Body Mass Index (BMI, weight/height) was calculated as weight in kilograms and height in square meters and compared to standard BMI charts based on age and gender (6).

Two questionnaires were used in order to obtain in the data (variables). The first questionnaire was about the feeding habits and socio-economic status of families and the second questionnaire was about mental health in children. Validity of questionnaire was approved by experts using "content validity "method, also its reliability was confirmed with the Test-Retest method with r=0.85 and r=0.78, respectively. Data collection was performed using phone interviews with parents, as well as the questionnaire's records. An analysis was done in SPSS16 software using appropriate statistical tools and tests, p value less than 0.05 was considered significant.

The study was approved by the ethical committee of Mazandaran University of Medical Sciences.

RESULTS

A total of 653 elementary school students 7-12 years old from Sari were studied, 297 (45.5%) of which were males and 356 (55.5 %) were females (Table 1).

Mean age in obese children was 8.93 ±33.4 years, and in non-obese children (95%> BMI) 9.63±3.6 years (p=0.002).

Table 1. School grades of examinees

Students level	Number (%) of children
1st grade	122 (18.7)
2nd grade	120 (18.4)
3rd grade	117 (17.9)
4th grade	141 (21.6)
5th grade	153 (23.4)
Total	**653 (100)**

The prevalence of overweight was higher in cases with highly educated parents (p=0.009). Significant relationship between school grade and obesity was found, though the obesity was more common in the first grade 25 (20.5%) and second 11 (9.2%) than other grades (p= 0.001) (Table 2).

Two hundred ninety four (45%) fathers and 502 (80.5%) mothers had a diploma or advanced diploma (Table 3).

Of 653 participants, 129 (20%) lived in leased house, 510 (78.9%) at their own home.

The coverage of insurance was evaluated in 624 (95.5%) cases, most of them had social support, healthcare, banking and military insurance, 502 (80.5%), 15 (2,4%) had rural insurance, 45 (7.2%) had supplemental insurance and 62 (9.9%) participants were without insurance.

The evaluation of socio economic state (SES), which represented a combined variable of parents educational level and occupation, as well as possession of the house and insurance coverage showed that 414 (63.4%) of children had moderate SES, and 239 (36.6%) good SES.

The prevalence of overweight and obesity in children with less than two hours exercise per week was 63.6%, and 36%, respectively (p=0.001(, and in children with more than two hours of exercise per week it was 26% and 11%, respectively (p=0.002(.

This study also showed a significant relationship between overweight obesity and the number of meals and fast food. Ninety 90 (13.8%) persons had three meals per day, 508 (77.9%) had four, and 54 (83%) had five meals per day. The prevalence of overweight and obesity in children who ate 3-4 meals per day was 18.4% (47) (p=0.000), and in children who ate five meals per day, 57.4% (31) (p=0.000).

Five hundred and seven (78%) persons ate fast-food less than two times a week, 138 (21.2%) 2- 4 times, and five (0.8%) persons more than 4 times per week. The prevalence of overweight and obesity was 21.8% (109) and 78.2% (392), respectively, in children who had fast food meals less than two times per week, whereas in children who had more than 2 times per week it was 47.1% (65children) (p=0.001), and 60% (3 children), respectively (p=0.002).

Junk food was eaten by 145 persons (22.4%) less than two times per week, 385 (59.6%) 2-4 times and 116 (18%) ate junk food more than 4 times per week. The prevalence of obesity in children who had this kind of food four times per week was 10.2% (12 persons), and in children with less than four times per week it was 16.7% (89cases) (p=0.004).

During the first 6 months of birth, 650 cases were assessed, 184 (28.3%) of them were breastfed exclusively during the first 6 months, and 65 (10%) had formula milk exclusively. There was no a significant relationship between obesity and overweight in the group of exclusively breastfed children in the first 6 months of life (p=0.87).

There was noted 177 (27.4%) overweight children (85% <BMI), and 78 (12%) were obese (95% <BMI).

In children with moderate SES the prevalence of overweight was 23% (151) and in children with good SES it was 34.9% (227) (p = 0.001). There were no significant relationship between overweight and possession of house and insurance coverage.

Table 2. Prevalence of overweight in relation to education

	The number (%) of children		
School grade of parents	**BMI>95%**	**BMI<95%**	**Total**
Grade 1	25 (20.5)	97 (79.5%)	122 (18.8)
Grade 2	11 (9.2%)	109 (90.8%)	120 (18.5)
Grade 3	15 (13%)	100 (87%)	115 (17.7)
Grade 4	22 (15.7%)	118 (84.3%)	140 (21.6)
Grade 5	5 (3.3%)	146 (96.7%)	151 (23.3)
Total	**78 (12%)**	**570 (88%)**	**648**

BMI, Body Mass Index

Table 3. Education level of parents

Parents	Level of Education	Number (%) of children
Father	Illiterate	3 (0.5)
	Elementary level or elementary degree	206 (31.5)
	Diploma or advanced diploma	294 (45)
	Bachelor of Science or Academic Degree	150 (23)
	Total	653 (100)
Mother	Illiterate	62 (9.9)
	Elementary level or elementary degree	15 (2.4)
	Diploma or advanced diploma	502 (80.5)
	Bachelor of Science or Academic Degree	45 (7.2)
Total		**624 (100)**

DISCUSSION

Childhood obesity has been seriously considered as a major issue and priority in the health system in developed countries especially in recent decades, and not only extensive studies have been performed about it, but also the programs based on national interventions have been designed and implemented. In recent years, it has gradually emerged as an important issue in developing countries, resulting in many published studies (3,7,8).

Seven- to twelve-year old students from Sari (Iran) were evaluated for overweight and obesity prevalence during the years 2009-2010, and according to the results 27.4% and 12%, respectively was found. According to a previous study in Iran the obesity of 4.8% in the same age, and 13.3% in the 6-11 years old children was noted (9), it indicated relatively high prevalence of overweight obesity in primary school students of Sari, compared to other Iranian cities.

The comparison of the findings of this study with other countries in the Middle East in the recent years has shown the higher prevalence of childhood overweight and obesity in our study than in Iraq (1.3% and 22.4%, respectively) (10), but lower prevalence compared to some other countries in our region, like the Emirates and Turkey (13.7% and 32%, respectively) (7, 11).

On the other hand, the prevalence of childhood obesity found in this study was almost similar to some developed regions/countries such as industrial cities of China (26%) (8).

Still, according to evidence mentioned above, the overall prevalence of obesity in studied children population in Iran was high, which suggests the need for serious attention to this issue in the view of health system, extensive studies, designing and implementation of interventions regarding childhood obesity.

The results of this study have not shown significant relationship between gender and obesity, which is in accordance with the results of some other studies (12,13), although there is data about higher prevalence of childhood obesity in boys (8,14), as well as in girls (15). These differences could be explained by sampling or cultural-economic conditions of the population (parents paying more attention to boys or girls). However, generally it seems that boys are at greater risk for obesity, and special attention to boys is essential in the childhood obesity control programs.

A strong relationship between obesity and reduced physical activity in this study was found. This finding is consistent with most studies (16,17), which indicated the computer games and watching TV for more than 6 hours per day as the reason for a lack of exercise, which was indicated as a risk factors for childhood obesity. In this regard, most academic scientific associations such as the America Heart Association (AHA) seriously recommend regular and continuous physical activity in childhood at least for 40-60 minutes per day as a preventive intervention (17). Moreover, some studies have documented such effects on decreasing prevalence of obesity in children (18).

Another important factor in prevalence of obesity in children is feeding habits, which depends on socio-economic and cultural context of communities. This issue has been considered in several studies and has also led to the development some strategies and extensive popular interventions. This study has shown the significant relationship between eating fast food and increased prevalence of overweight and obesity in children, which is consistent with the study of Karam et al. in Yazd (Iran), which has shown high calorie food as one of the most important factors in childhood obesity (19). In a number of studies it was also found that fast food, high-calorie packaged food and reduced eating of vegetables and fruits are important causes of childhood obesity (11,15,16,20).

Limitations of this study included selecting samples from urban communities, survey of feeding habits and physical activity based on self-administered questionnaires and a cross-sectional study design.

In conclusion, this study demonstrates high prevalence of obesity in children aged 7-12 years in Sari, that it is significantly related to eating fast food, meals frequency, and decrease of exercises. This study indicates the need for serious attention to the issue of childhood obesity, performance of more extensive studies, identification of underlying factors precisely and designing the implementation of needed interventions.

AKNOWLEDGEMENT

Authors appreciate the students, school administrators and education officials' cooperation in Sari.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Colombo O, Villani S, Pinneli G, Trentani C, Baldi M, Tomarchio O, Tagliabue A. To treat or not to treat:comparison of different criteria used to determine whether weightloss is to be recommended. Nutr J 2008, 7:5-11.
2. Ogden CL,Yanovski SZ,Carroll MD,Flegal KM.The epidemiology of obesity. Gastroenterolog 2007, 132:2087-102.
3. Kelishadi R, Ardalan G, Gheiratmand R, Majdzade R, Hosseini M, Gouya MM, Mahmoud-Arabi MS, Lock K. Thinness, overweight and obesity in a national sample of Iranian children and adolescents. CASPIAN study. Child care health Dev 2008; 34:44-54.
4. Krebs NF, Primak LE. Pediatric Nutrition and Nutritional Disorder. In: Marcdante K, Kliegman R, Behrman R, Jenson H, eds. Nelson Essentials of Pediatrics 2010. 6th ed. Philadelphia: Sounders Elsevier, 2011:109-10.
5. AkhaO,Teymourzade M, Kashi Z, Kousarian M. A Study on 6-18 Years- Old Girl Students about Weight and Height in Sari. Journal of Mazandaran University of Medical Sciences, 2009; 18:50-7.
6. Dawson P. Normal growth and revised growth charts. Pediatr Rev 2002; 23:255 -6.
7. Malik M, Bakir A. Prevalence of overweight and obesity among children in the United Arab Emirates. Obes Rev 2007; 8:15-20.
8. Ji CY, Cheng TO. Prevalence and geographic distribution of childhood obesity in China in 2005. Int J Cardiol 2008; 131:1-8.
9. Haeri Behbahani B, Dorosty A.R, Eshraghian M.R. Assessment of obesity in children: fat mass index versus body mass index Tehran. University Medical Journal 2009; 67:408-14.
10. Lafta RK, Kadhim MJ. Childhood obesity in Iraq: prevalence and possible risk factors. Ann Saudi Med 2005; 25:389-93.
11. Garipagaoglu M, Budak N, Süt N, Akdikmen O, Oner N, Bundak R. Obesity risk factors in Turkish children. J Pediatr Nurs 2009; 24:332-7.
12. khaji A, Khoaii Sh, Karbakhsh M, Faeghi A, Azizi S, Firuzian A, Jafari J. Blood pressure and obesity in young adolescents in Tehran. Iran J Pediatr 2006; 16: 49.
13. Zimmermann MB, Gübeli C, Püntener C, Molinari L. Overweight and obesity in 6-12 year old children in Switzerland. Swiss Med Wkly 2004; 134:523-8.
14. El-Bayoumy I , Shady I, Lotfy H. Prevalence of obesity among adolescents (10 to 14 Years) in Kuwait. Asia Pac J Public Health 2009; 21: 153-9.
15. Jian-Meng Liu , Rongwei Ye, Song Li, Aiguo Ren, Zhiwen Li, Yinghui Liu, Zhu Li. Prevalence of overweight/obesity in Chinese children. Arch Med Res 2007; 38:882-6.
16. Sluijs EM, Skidmore PM, Mwanza K, Jones AP, Callaghan AM, Ekelund U, Harrison F, Harvey I, J Panter, Wareham N J, Cassidy A, Griffin S J. Physical activity and dietary behaviour in a population-based sample of British 10-year old children: the SPEEDY study (Sport, Physical activity and Eating behaviour: Environmental Determinants in Young people). BMC Public Health 2008; 8:388.
17. Hare-Bruun H, Nielsen BM, Kristensen PL, Mřller NC, Togo P, Heitmann BL. Television viewing, food preferences, and food habits among children: A prospective epidemiological study. BMC Public Health. 2011; 13:311.
18. Olds T, Maher CA, Ridley K, The place of physical activity in the time budgets of 10- to 13-year-old Australian children. J Phys Act Health. 2011; 8:548-57
19. Karam soltani Z, Dorosty motlagh AR, Eshraghian MR, Siassi F, Djazayeri, Obesity and food security in Yazd primary school students. Tehran University Medical Journal 2007, 65: 68-76
20. Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, Mihatsch W, Moreno LA, Puntis J, Shamir R, Szajewska H, Turck D, van Goudoever J; Role of Dietary Factors and Food Habits in the Development of Childhood Obesity: A Commentary by the ESPGHAN Committee on Nutrition.J Pediatr Gastroenterol Nutr. 2011;52:662-669.

ORIGINAL ARTICLE

Chemometric analysis of groundwater quality data around municipal landfill and paper factory and their potential influence on population's health

Vlatka Gvozdić[1], Ljiljana Čačić[2], Josip Brana[3], Dinko Puntarić[4], Domagoj Vidosavljević[5]

[1]Department of Chemistry, University JJ Strossmayer Osijek, [2]Vodovod-Osijek, [3] Department of Physic, University JJ Strossmayer Osijek; Osijek, [4]Department of Health Ecology, Public Health Institute, Zagreb, [5]Vukovar General Hospital, Vukovar; Croatia

ABSTRACT

Aim To assess the level of 15 groundwater quality parameters in groundwater samples collected around municipal landfill and paper factory in order to evaluate usefulness of the groundwater and its possible implication on the human health.

Methods Obtained data have been analyzed by principal component analysis (PCA) technique, in order to differentiate the groundwater samples on the basis of their compositional differences and origin.

Results Wastes and effluents from municipal landfill did not contribute significantly to the pollution of the aquatic medium. Groundwater degradation caused by high contents of nitrate, mineral oils, organic and inorganic matters was particularly expressed in the narrow area of the city centre, near the paper factory and most likely it has occurred over a long period of time. The results have shown that the concentrations of the most measured parameters (NO_3-N, NH_4-N, oils, organic matter, Fe, Pb, Ni and Cr) were above allowed limits for drinking and domestic purposes.

Conclusion This study has provided important information on ecological status of the groundwater systems and for identification of groundwater quality parameters with concentrations above allowable limits for human consumption. The results generally revealed that groundwater assessed in this study mainly does not satisfy safe limits for drinking water and domestic use. As a consequence, contaminated groundwater becomes a large hygienic and toxicological problem, since it considerably impedes groundwater utilization. Even though, all of these contaminants have not yet reached toxic levels, they still represent long term risk for health of the population.

Key words: ground water, quality, pollution, Principal Component Analysis

Corresponding author:
Vlatka Gvozdić,
Faculty of Chemistry, University JJ Strossmayer Osijek
Kuhačeva 20, 31000 Osijek, Croatia
Phone: +385 31 495 533,
fax: +385 31 495 549;
E-mail: vlatka.gvozdic@kemija.unios.hr

Original submission:
05 April 2011;
Revised submission:
27 August 2011;
Accepted:
August 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):91-96

INTRODUCTION

The surface and groundwater contamination have become one of the main sources of health related problems (1, 2). The results of investigation of the appearance of diseases linked to contaminated water in Croatia since 1981 have shown that gastroenterocollitis, bacillary dysentery, hepatitis and gastroenteritis predominated; while leptospirosis and Legionnaire's disease were less present (1,3). The recent studies indicate that the water of the Lower Drava River meet only the standards for the Class III and as such is not suitable raw material for production of drinking water (4). Unfortunately, ground waters in eastern Croatia are troubled with As, Fe, Mn, ammonia and natural organic material (5, 6). Despite the well known fact that chronic arsenic exposure has been associated with a variety of cancers as well as skin changes and high iron content in water is related with higher risk of developing inflammatory bowel disease, ground waters are still the main sources of drinking water in the area of eastern Croatia (7, 8). Beside arsenic contamination, long-term exposure to other chemical contaminants such as nitrate, Cr, Pb, Cd and polyaromatic hydrocarbons (PAHs), may also lead to environmental and health problems (9-14). Since food chain contamination is one of the major routes for entrance for various contaminants into the human system, groundwater monitoring and assessment always generate a lot of interest. (15-18). In the long run, chemical and microbial pollution can contaminate the groundwater, soil, crops, food, vegetables and fruits and may cause considerable adverse impact on health of the local population and final consumers (19-24). The purpose of the present study was to evaluate variables/sources responsible for groundwater quality in samples collected at different distances from the landfill and paper mill through the application of principal component methods (PCA) technique (25). Further, the objective of this study was to assess possible groundwater pollution due to landfill and paper mill in urban and suburban area in order to prevent and avoid health risks.

MATERIALS AND METHODS

Study area

The industrial town of Belišće in eastern Croatia is located at 45.68ºN and 18.41ºE at the right bank of the Drava river at latitude of 92m with a population of about 7200. The municipal landfill covers the area of 32 000 m^2 and it has been active since 1980; paper mill since 1960. Agricultural (vegetable gardens, orchards and meadows), cattle farming and industrial activities (paper industry) are carried out in the area. Map of investigated area with locations of thirteen sampling sites (hand pumps) is shown in Fig.1.

Sampling and chemical analysis

The water samples were selected in such a manner as to represent the whole study area around the landfill and paper mill. The ground water samples were taken by means of hand pumps (from the depth of 15-20 metres) after a pumping period of at least 15 minutes in order to remove stagnant water. Analyses were performed immediately after sample collection, using atomic absorption spectrometry methods to determine the concentrations of Cd, Cr, Cu, Fe, Pb, Ni and Zn. Chemical oxygen demand (COD) was measured by titration method while electrical conductivity and pH by electrochemical method. NH_4-N, NO_2-N and NO_3-N were determined spectrophotometrically, total organic carbon (TOC) and oils (Oils) by using TOC analyser and IR-spectroscopy method respectively. All the groundwater quality parameters are expressed in mgL^{-1}, except pH, EC (μScm^{-1}) and COD (mgO_2L^{-1}). The analysis of various water samples from different locations were carried out, according to the standards of the International Organization for Standardization (ISO) (26). Today's legislation in the Republic of Croatia regulates standards for drinking water quality, maximum allowed concentrations for some toxic substances, water use and protection (27).

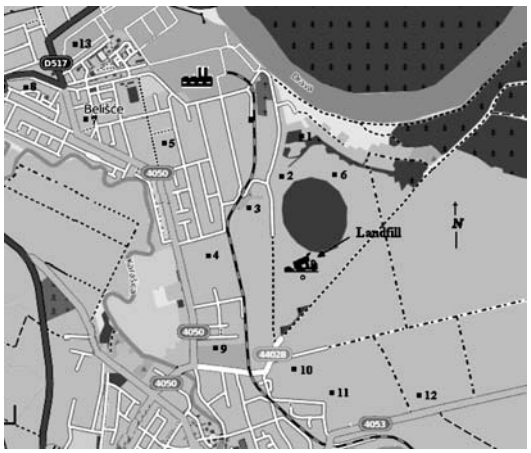


Figure 1. Map of Belišće area with locations of 13 measurement places

Statistical procedures

Besides standard descriptive statistics, PCA was performed. The data contain 15 groundwater quality parameters but 12 of them were selected for PCA because of their higher concentrations in groundwater samples.

RESULTS

Groundwater chemistry

Results for NO_3-N, NO_2-N and NH_4-N are converted and reported in Table 1 as NO_3^- (nitrate), NH_4^+ (ammonia) and NO_2^- (nitrite). Table 1 contains some descriptive statistics for fifteen groundwater chemical variables. Highest variability was noted for NO_3^- and EC. In addition, the obtained maximum EC and NO_3^- values were above the maximum allowed value for drinking water. The maximum values of oils, EC, COD, NH_4^+, Ni, Fe, Cr and Pb were also above the maximum allowed concentrations determined by Croatian standards. The concentrations of remaining variables (pH, NO_2, Cd, Cu and Zn) were within normal range of values and have shown little variations. Groundwater samples were circumneutral, with pH ranging from 7.02 to 7.85. The approximate location of the source of organic waste inputs and the extent of ground-water degradation were delineated by the TOC values. The TOC values showed high variability and deviations from median values.

Principal Component Analysis

The obtained data were subjected to the PCA in order to define virtual variables which will describe their interdependence. PCA, followed by varimax rotation method, provides the results given in Fig. 2 (so-called biplot).

Table 1.Descriptive statistics of the 15 groundwater quality parameters measured at 13 measurement sites located in the Belišće area

Variables	M.A.C.	Mean	Minimum	Maximum	S.D.
pH	6.5-9.5	7.311	7.020	7.850	0.211
Oils	0.02	0.899	0.3392	3.478	0,835
NH_4^+	0.50	3.321	0.0058	16.872	5.629
NO_2^-	0.50	0.054	0.0039	0.331	0.086
NO_3^-	50.0	38.504	0.0199	232.999	75.41
EC	2500	1257.077	517.000	2879.000	715.0
Cd	0.005	0.001	0.001	0.002	0.000
Cr	0.05	0.021	0.0010	0.057	0.020
Ni	0.02	0.005	0.0009	0.027	0.007
Pb	0.01	0.018	0.0045	0.039	0.013
Cu	2	0.008	0.0009	0.051	0.013
Zn	3	0.114	0.0060	0.434	0135
Fe	0.2	1.443	0.0190	7.325	2.097
TOC	*	2.727	1.2100	10.120	2.415
COD	5	3.077	1	9	2.46

S.D., standard deviation; M.A.C., maximum allowed concentrations; *values should not significantly deviate from the mean values

Three main clusters of samples could be distinguished: a rather compact cluster in the left portion of Fig. 2 which contains most samples (zone 3). It therefore defines the most common conditions, i.e. determines situations that are more frequent. Since the variables that point toward certain objects are more important for those objects, it is obvious that variables NH_4^+ and NO_2^- are important for these measuring sites. While the measuring sites 2 and 6 in the right portion of Fig. 2 display the sites with highest variations in EC and metal concentrations (zone 2), central cluster (zone1) contains TOC, COD, Fe, oils, pH and NO_3^-, and groundwater samples: 3,4,5 and 7. Consequently, these two clusters represented less frequent cases.

DISCUSSION

The three zones were identified using principal component analysis technique. Zone 1 consisted of highly polluted sites which were restricted to the places in the vicinity of paper factory and city centre area. In these samples a considerable amount of mineral oils, nitrate and Fe were found, even 170, 5 and 37 times grater than maximum allowable concentrations regulated by Croatian regulative for drinking waters. It is notable that samples in this zone were polluted with chemical contami-

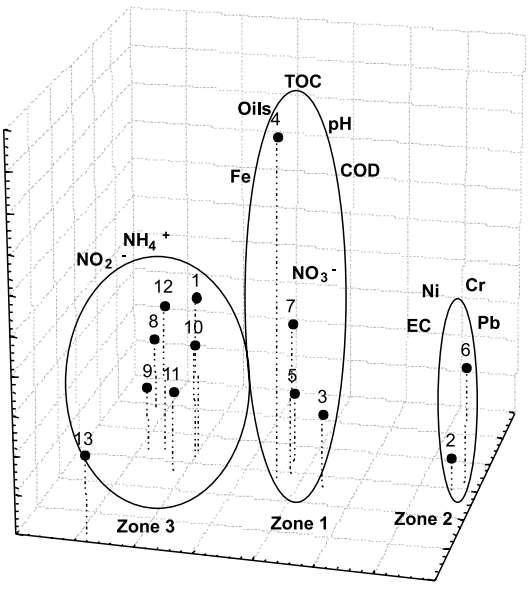


Figure 2. Plot of scores and loadings of 13 groundwater samples characterized by 12 chemical parameters (EC, pH, TOC, Oils, COD, NH_4^+, NO_3^-, NO_2^-, Ni, Fe, Cr, Pb). Numbered points refer to the corresponding measurement sites distributed in three different clusters (zones)

nants of industrial origin and results demonstrate a significant influence of anthropogenic activities on the aquatic media. Further, results have shown that significant organic and oil groundwater contamination did occur at distance of about 500 m from the paper mill plants. Vegetable growing on soil contaminated by gasoline or diesel fuel may contain carcinogenic chlorinated or hydrocarbon pollutants in their tissues at significant concentrations (10, 28). Irrigation with such degraded water might result in build-up of the elevated concentrations especially due to long-term use. Elevated concentrations of other relevant chemical pollutants such as nitrate, also lead to pollution problems (23). Based on methaemoglobinaemia in infants (an acute effect), the WHO has established a guideline value for nitrate ion of 50 mgL^{-1} as NO_3^- (29). The nitrate concentration higher than 10 mgL^{-1} may cause nitrate poisoning of infants during the first months of life (blue-baby syndrome) but chronic ingestion of smaller doses can contribute to the risk of non-Hodgkin's lymphoma, colon cancer, dyspepsia and mental depression (24, 30,31). Recent studies showed that higher levels of the nitrate and nitrite in edible portions of some leafy vegetables are indicators of possible pollution as a result of excessive usage of fertilizers and irrigation with polluted water (16, 32). The levels of pollutants (other than heavy metals) measured in less populated zone 2 located in the vicinity of landfill were low in comparison to levels on other two zones, which is to some extent related to the dilution effect of the Drava River water.

However, the heavy metal values observed in samples from this study were much higher in comparison with their typical concentrations in natural groundwater (33). Heavy metals are very harmful because of their non-biodegradable nature, and they have potential to accumulate in different body parts and even low concentrations have damaging effects to people and animals. (12). Heavy metals often form a part of the active compounds of pesticides and superphosphate fertilizers (32). Approximately 20% of human exposure to lead is attributable to lead in water, which is cumulative poison, initiating irritability, anaemia and tiredness (9).

The most of the samples in this study with elevated ammonia concentrations were located in suburban parts of the observed area where septic tanks and manure storages are situated and poultry farming is still a common practice. Ammonia in the environment mainly results from on-site sanitation (septic tanks or primitive toilets) and leaking sewers, thus concentrations higher than 0.2 mgL^{-1} in groundwater are mostly indicators of sewage pollution (29, 33,34). In some samples the maximum values for ammonia were even thirty times more than prescribed by the permitted values of Croatian standard for drinking water. Although ammonia in drinking water is not of direct health relevance, bacteria and viruses from human and animal wastes carried to groundwater can cause disease (33,35,36). The results generally revealed that groundwater assessed in this study mainly does not satisfy safe limits for drinking and domestic use.

It would be desirable to obtain some other data for groundwater in the wider area of eastern part of Croatia, but there are either no data or the existing data are not comparable because in this pioneering study the samples were collected in completely different ways and in different locations. Further extended studies are certainly needed to estimate possible occurrence of any adverse health effects in the populations.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Vitale K, Marijanović Rajčić M, Senta A. Waters in Croatia between practice and needs: Public health challenge. Croat Med J 2002; 43: 485-492.
2. Gleick P. Dirty water: estimated deaths from water-related diseases 2000-2020. Pacific Institute Research Report, 2002. www.pacinst.org (15.2.2011.)
3. O' Reilly CE, Bowen AB, Perez NE, Sarisky JP, Shepherd CA, Miller MD, Hubbard BC, Herring M, Buchanan SD, Fitzgerald CC, Hill V, Arrowood MJ, Xiao LX, Hoekstra RM, Mintz ED, Lynch MF, Outbreak Working Group. A waterborne outbreak of gastroenteritis with multiple etiologies among resort island visitors and residents: Ohio, 2004.Clin Infect Dis 2007; 44: 506-512.
4. Mijušković-Svetinović T. Estimating the water quality of river Drava. In: Proceedings of the XIX th conference of the Danube countries on hydrological forecasting and hydrological bases of water management; 1998 Jub 15-19; Osijek, Croatia.

5. Habuda-Stanić M, Kuleš M. Arsenic in drinking water [in Croatian]. Kem Ind 2002; 51: 337-342.
6. Habuda –Stanić M, Kuleš M, Kalajdžić B, Romić Z. Quality of groundwater in eastern Croatia. The problem of arsenic pollution. 2007; Desalination 2007; 210: 157-162.
7. Tchounwou PB, Patlolla AK, Centeno JA. Carcinogenic and systemic health effects associated with arsenic exposure-a critical review. Toxicol Pathol 2003; 31: 575-588.
8. Aamodt G, Bukholm G, Jahnsen J, Moum B, Vatn MH, IBsen Study Group. The association between water supply and inflammatory bowel disease based on a 1990-1993 cohort study in southeastern Norway. Am J Epidemiol 2008;168: 1065-1072.
9. Jordana S, Batista E. Natural groundwater quality and health. Geol Acta 2004; 2: 175-188.
10. T ao S, Cui YH , Xu FL, Li BG, Cao J, Liu WX, Schmitt G, Wang XJ, Shen WR, Qing BP, Sunb R. Polycyclic aromatic hydrocarbons (PAHs) in agricultural soil and vegetables from Tianjin.Sci Tot Environ 2004; 320: 11-24.
11. Wang X, Sato T, Xing B, Tao S. Health risks of heavy metals to the general public in Tianjin, China via consumption of vegetables and fish. Sci Total Environ 2005; 350: 28-37.
12. Arora M, Kiran B, Rani S, Rani A, Kaur B, Mittal N. Heavy metal accumulation in vegetables irrigated with water from different sources. Food Chem.2008; 111: 811-815.
13. Luo C, Liu C, Wang Y, Liu X, Li F, Zhang G, Li X. Heavy metal contamination in soils and vegetables near an e-waste processing site, south China. J Hazard Mater 2011; 186: 481-490.
14. Adeyemi O, Oloyede OB, Oladiji AT. Biochemical evaluation of leachate contaminated groundwater on the kidney of Albino rats. Exp Toxicol Pathol 2010; 62 : 483-488.
15. Al Sabahi E, Abdul Rahim S, Wan Zuhairi WY, Al Nozaily F, Alshaebi F. The characteristics of leachate and groundwater pollution at municipal solid waste landfill of Ibb City, Yemen. Am. J Environ Sci 2009; 5: 256-266.
16. Uwah EI, Ndahi NP, Ogugbuaja VO. Study of the levels of some agricultural pollutants in soils and water leaf (*Talinum Triangulare*) obtained in Maiduguri, Nigeria. J Appl Sci Environ Sanit 2009; 4: 71-78.
17. Rattan RK, Datta SP, Chhonkar PK, Suribabu K, Singh AK. Long-term impact of irrigation with sewage effluents on heavy metal content in soils, crops and groundwater-a case study. Agric Ecosyst Environ 2005; 109: 310-325.
18. Singh KP, Malik A, Singh VK, Mohan D, Sinha S. Chemometric analysis of groundwater quality data of alluvial aquifer of Gangetic plain, North India. Anal Chim Acta 2005; 550: 82-91.
19. Rosas I, Belmonti R, Armienta A, Baez A. Arsenic concentrations in water, soil, milk and forage in Comarca Lagunera, Mexico. Water Air Soil Pollut 1999; 112: 133-149.
20. Jergović M, Miškulin M, Puntarić D, Gmajnić R, Milas J, Sipos L. Cross-sectional biomonitoring of metals in adult populations in post-war Eastern Croatia: Differences between areas of moderate and heavy combat. Croat Med J 2010; 51: 451-460.
21. Uwah EI,Abah J, Ndahi NP, Ogugbuaja VO. Concentration levels of nitrate and nitrite in soils and some leafy vegetables obtained in Maiduguri, Nigeria. J Appl Sci Environ Sanit 2009; 4: 233-244.
22. Hamilton AJ, Stagnitti F, Premier R, Boland AM, Hale G. Quantitative microbial risk assessment models for consumption of raw vegetables irrigated with reclaimed water. J Appl Microbiol 2006; 72: 3284-3290.
23. Okafor PN, Ogbonna UI. Nitrate and nitrite contamination of water sources and fruit juices marketed in South-Eastern Nigeria. J Food Compos Anal 2003;16: 213–218.
24. Van Grinsven, Rabl A, De Kok T. Estimation of incidence and social cost of colon cancer due to nitrate in drinking water in the EU: a tentative cost-benefit assessment. Environ Health 2010; 9: 58-70.
25. Vandeginste BGM, Massart DL, Buydens LMC, De Jong S, Lewi PJ, Smeyers-Verbeke J. Handbook of Chemometrics and Qualimetrics (Part A). Amsterdam, Elsevier1998: 519-556.
26. International Organization for Standardization (ISO), TC 147 Water quality-part 2; physical, chemical and biochemical methods.Available at:http://www.iso.org
27. Ministry of Health, Republic of Croatia. Regulation for drinking water safety [in Croatian]. Narodne Novine 2008; No 47.
28. Pawlak Z, Rauckyte T, Oloyede A. Oil, grease and used petroleum oil management and environmental economic issues. Journal of Achievements in Materials and Manufacturing Engineering 2008; 26: 11-17.
29. World Health Organisation (WHO) Water Quality Assessments - A Guide to Use of Biota, Sediments and Water in Environmental Monitoring -Second Edition. http://www.who.int/water_sanitation_health/resourcesquality/watqualassess.pdf
30. Knobeloch L, Salna B, Hogan A, Postle J, Anderson H. Blue babies and nitrate-contamined well water. Environ Health Perspect 2000; 108: 675-678.
31. Ward MH, Mark SD, Cantor KP, Weisenberger DD, Correa-Villaseñor A, Zahm SH. Drinking water nitrate and the risk of non- Hodgkin's lymphoma. Epidemiology1996; 7: 465-471.
32. Gimeno-Garzía E, Andreu V, Boluda R. Heavy metals incidence in the application of inorganic fertilizers and pesticides to rice farming soils. Environ Poll1996; 92:19-25.
33. World Health Organization (WHO). Protecting Groundwater for Health, Managing the Quality of Drinking-water Sources, 2006.
34. Böhlke JK, Smith RL, Miller DN. Ammonium transport and reaction in contaminated groundwater: Application of isotope fractionation studies. Water Resour Res 2005; 42, WO5411, Doi:10.1029/2005WR004349.
35. Hamilton AJ, Stagnitti F, Premier R, Boland AM, Hale G. Quantitative microbial risk assessment models for consumption of raw vegetables irrigated with reclaimed water. J Appl Microbiol 2006; 72: 3284-3290.
36. Dhakyanaika K, Kumara P. Effects of pollution in River Krishni on hand pump water quality. Journal of Engineering Science and Technology Review 2010; 3: 14-22.

Kemometrijska analiza kvalitete podzemne vode na području odlagališta komunalnog otpada i tvornice papira, te njihov mogući utjecaj na zdravlje stanovništva

Vlatka Gvozdić[1], Ljiljana Čačić[2], Josip Brana[3], Dinko Puntarić[4], Domagoj Vidosavljević[5]

[1]Odjel za kemiju, Sveučilište ž'J. J. Strossmayer'', Osijek, [2]Vodovod, Osijek, [3]Odjel za fiziku, Sveučilište ž'J. J. Strossmayer'', Osijek, [4]Odjel za zdravstvenu ekologiju, Zavod za javno zdravstvo grada Zagreba, Zagreb, [5]Opća bolnica Vukovar; Hrvatska

SAŽETAK

Cilj Utvrditi vrijednosti 15 parametara kakvoće u uzorcima podzemnih voda, prikupljenim oko komunalnog odlagališta otpada i tvornice papira, kako bi se procijenio stupanj zagađenja i moguće posljedice na ljudsko zdravlje.

Metode Dobiveni podaci su analizirani metodom analize glavnih komponenata (PCA), kako bi diferencirali podzemne uzorke na temelju njihovog sastava i podrijetla.

Rezultati Otpad i otpadne vode iz odlagališta komunalnog otpada nisu značajno doprinosili zagađenju vodenih medija. Podzemno onečišćenje, uzrokovano visokim sadržajem nitrata, mineralnih ulja, organskim i anorganskim spojevima, osobito je bilo izraženo u uskom području centra grada, u blizini tvornice papira, a vjerojatno je posljedica onečišćenja koje se dogodilo tijekom dužeg vremenskog razdoblja. Koncentracije većine mjerenih parametara (NO_3-N, NH_4-N, ulja, organska tvar, Fe, Pb, Ni i Cr) bile su iznad dopuštene granice za humanu uporabu.

Zaključak Ova studija je poslužila za stjecanje važnih informacija o stanju eko sustava podzemnih voda i za određivanja parametara kvalitete podzemnih voda (u ovom slučaju, s koncentracijama iznad dopuštene granice za ljudsku uporabu). Rezultati su općenito pokazali da podzemne vode u ovom istraživanju, uglavnom nisu zadovoljavale kriterije ispravnosti za pitku vodu i korištenje u kućanstvima. Kao posljedica toga, kontaminirane podzemne vode postaju veliki ekološki i toksikološki problem. Iako onečišćenje nije dostiglo toksičnu razinu, ono ipak predstavlja trajnu opasnost za zdravlje populacije.

Ključne riječi: podzemne vode, kvaliteta, zagađenje, analiza glavnih komponenata

ORIGINAL ARTICLE

Soil chemicals properties and wheat genotype impact on micronutrient and toxic elements content in wheat integral flour

Zdenko Lončarić[1], Brigita Popović[1], Krunoslav Karalić[1], Zorica Jurković[2], Ante Nevistić[3], Meri Engler[1]

[1]Faculty of Agriculture, University J.J. Strossmayer Osijek, Osijek, [2]Croatian Food Agency, Osijek, [3]Inspecto Ltd., Đakovo; Croatia

ABSTRACT

Aim To determine impact of soil chemical properties and different wheat genotypes in Croatia on micronutrient and toxic elements content in wheat integral flour.

Methods Research was conducted and soil samples were collected from two different production areas in the Republic of Croatia: Ovčara and Dalj. Besides soil samples, grain samples of four different Croatian wheat genotypes were also collected and analyzed. In total, 40 samples of soil and 40 samples of wheat grain were analysed for total (aqua regia) and plant available (EDTA extraction) heavy metal content of Fe, Mn, Zn, Cu, Pb, Cd.

Results Determined soil pH_{KCl} ranged from 5.63 to 6.25 at Ovčara and from 6.95 to 7.37 at Dalj sampling sites. The highest total concentration of heavy metals in soil were determined for Fe, followed by Mn, Zn, Cu, Pb and the lowest total concentration was recorded for Cd. The highest EDTA concentrations in soil were determined for Mn, than followed by Fe, Cu, Pb, and the lowest EDTA concentration was recorded for Cd. The highest concentration in integral wheat flour was found for Fe, than lower for Mn, Zn, Cu, Pb and the lowest concentration was found for Cd. If consumers in Croatia used daily 203 g of bread made of integral flour, they would take 2.31 to 8.44 μg Cd daily, depending on soil and wheat genotype.

Conclusion The analysed soil and winter wheat genotypes have significant impact on potential daily intake of toxic and essential heavy metals by integral flour or bread.

Key words heavy metals, soils, wheat genotypes, integral flour

Corresponding author:
Brigita Popović
Faculty of Agriculture, University J.J. Strossmayer Osijek
Trg Sv. Trojstva 3, 31000 Osijek, Croatia
Phone: +385 31 22 42 57;
fax: +385 31 20 70 17;
E-mail: brigita.popovic@pfos.hr

Original submission:
15 April 2011;
Revised submission:
29 June 2011;
Accepted:
September 07 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):97-103

INTRODUCTION

The concept of heavy metals includes metals with density greater than 5g/cm^3. A variety of these metals in the form of trace elements are necessary - essential for many functions in the human body and their deficiency leads to severe deficiency symptoms (1). The presence of mineral elements, such as Fe, Zn, Cu, Mn (often called micronutrients) are crucial for human health as organic compounds such as carbohydrates, fats, protein and vitamins (1). For other elements such as Pb, Cd, Co, Hg, As and Ni it has been shown that large quantities produce toxic effects because they tend to accumulate in the body, vital organs and tissues (brain, liver, spleen, pancreas), thereby disrupting their normal functions (2). They also displace „good“ minerals (Mn, Zn, etc.) that are necessary for vital enzyme reactions (2). In general, some heavy metals have no function in the body and can be highly toxic. They are systemic toxins with specific neurotoxin, nephrotoxic, phototoxic and tetratogenic effects (3).

As a result of soil, atmosphere, underground and surface water pollution, foods and beverages are getting contaminated by heavy metals (4). The major route for heavy metals exposure to humans is mainly through soil–crop–food pathway . The residual plant components, including hull, straw and the root are partly returned to the soil and partly used as an ingredient in food for livestock, which is also a possible pathway for heavy metals to enter the human body by ingesting contaminated food (5,6). The largest amount of heavy metals found in human body has been absorbed via food partly through wheat flour and bread because wheat bread is an important diet cereal product that provides as much as 50-90 % of total caloric and protein intakes (5,6). The task of agricultural production is, on one hand, to increase the absorption of micronutrients (Zn, Fe, Mn, Cu) in wheat grain and on the other hand, to reduce the absorption of toxic elements (Cd, Pb, Hg) (7). The contents of micronutrients in food can be elevated either by supplementation, fortification or by agricultural strategies such as bio fortification and application of micronutrients containing fertilizers (7). Food fortification and supplements are too expensive, not practical to be applied on large scale and not easily accessible to the poor (8). The development of micronutrients efficient genotypes can be a successive tool to overcome the micronutrient disorders in soil and for improvement of human health (8).

The aim of this study was to determine impact of soil chemical properties and different wheat genotypes in Croatia on micronutrient and toxic elements content in wheat integral flour.

MATERIALS AND METHODS

Research was conducted and soil samples were collected from two different production areas: Ovčara and Dalj in Republic of Croatia. Each locality has different soil properties, especially in terms of soil pH and heavy metal content. Soil on Ovčara production area was slightly acid and soil on production area Dalj was neutral to slightly calcareous. Samples were collected on five locations in each production area.

Besides soil samples, plant samples were also collected and analyzed, particularly grain of four different Croatian wheat genotypes: Cultivar 1- yield high, quality low; Cultivar 2-yield medium, quality medium; Cultivar 3-yield low, quality high; Cultivar 4- yield medium, quality medium. In total, 40 samples of soil and 40 samples of wheat grain were analysed to determine total heavy metal content (aqua regia) and plant available heavy metal content (EDTA extraction) (9,10).

All soil samples were analysed in the laboratory of Inspecto Company Ltd. to determine soil pH and total and plant available concentration of Fe, Mn, Zn, Cu, Cd, Pb (11). Concentration of Fe, Mn, Zn, Cu and Pb were determined by atomic absorption spectrophotometer (AAS) technique and concentration of Cd was determined by graphite furnace AAS technique (9,10).

Grain samples were analysed after microwave digestion and concentrations of Fe, Mn, Zn, Cu, Cd and Pb in wheat integral flour were determined by inductively coupled plasma (ICP), optical emission spectrometry (OES) technique (12). These analyses were conducted in the laboratory of the Department of Agroecology, Faculty of Agriculture in Osijek.

A statistical analysis was performed by SAS Program for Windows (SAS Institute INC., Cary, NC, USA). Statistic significance was determined by using the ANOVA test.

Table 1. Soil pH, total and plant available heavy metal concentrations in analysed samples

	Soil pH		total concentration (aqua regia) (mgkg^{-1})						available concentration (EDTA) (mgkg^{-1})					
Production area	pHH2O	pHKCl	Fe	Mn	Zn	Cu	Pb	Cd	Fe	Mn	Zn	Cu	Pb	Cd
Ovcara 1	7.07	5.95	26120	766.78	76.44	22.8	25.66	0.389	52.28	33.48	1.64	4.62	2.56	0.027
Ovcara 2	7.01	5.85	25900	686.9	79.34	23.10	23.48	0.367	67.04	37.46	1.76	4.24	2.32	0.0252
Ovcara 3	7.01	6.05	25980	641.62	76.84	25.18	24.32	0.435	50.84	51.56	1.44	4.54	2.52	0.043
Ovcara 4	7.16	5.87	25700	285.78	80.50	28.72	25.16	0.3866	33.28	13.92	1.68	5.12	4.70	0.051
Dalj 1	7.96	6.98	25520	755.58	76.14	26.28	21.74	0.3398	12.44	41.1	1.54	5.6	3.42	0.037
Dalj 2	7.93	7.02	26300	655.04	79.52	25.66	19.24	0.378	14.44	41.28	0.94	5.08	2.98	0.041
Dalj 3	8.30	7.21	25640	690.18	75.56	24.82	16.52	0.3766	12.04	29.66	0.8	4.46	2.04	0.013
Dalj 4	8.38	7.28	23540	744.02	86.18	30.56	15.6	0.423	6.82	24.82	1.08	5.34	2.114	0.028

RESULTS

Determined soil pH_{KCl} ranged from 5,63 to 6,25 at Ovčara production area and from 6,95 to 7,37 at Dalj production area (Table 1).

The highest total concentration of heavy metals was determined for Fe, followed by Mn, Zn, Cu, Pb and the lowest total concentration was recorded for Cd (Table 2).

EDTA concentration was slightly different and the highest EDTA concentration were determined for Mn, followed by Fe, Cu, Pb, whereas the lowest EDTA concentration was recorded for Cd (Table 2).

Furthermore, it was found that acid soils contained a significantly higher average concentration of total Fe, Mn and Pb than calcareous soils. As opposed to those results, higher concentration of Cu was found in calcareous soils. Concentration of total Zn and Cd were approximate in acid and carbonate soils and there was no statistically significant difference between them (Table 2).

Results show a significantly higher concentration of EDTA extracted Fe, Zn and Cu in average for acid soils as compared to calcareous soils, and significant difference among soils was not found for Mn, Pb and Cd (Table 2).

Different wheat genotypes have been grown on experimental localities and soils. Genotype Cultivar 4 was grown on soils with the lowest average total concentration of Fe and Mn but the highest total Cu concentration. Other three genotypes were grown on soils with similar Fe, Mn and Cu concentrations. Differences between grown genotypes and soil properties were determined for Cd between Cultivar 3 and Cultivar 4 (soil with higher concentration of total Cd) and Cultivar 2 as well as Cultivar 1 (soil with lowest total Cd) (Table 3, Table 4).

The soil conditions considering analysed wheat genotypes were different for all analyzed elements, except Cd. Cultivar 4 was grown on soils with the highest concentrations of EDTA extracted Pb and Cu, Cultivar 3 was grown on soils with high EDTA extracted Mn concentration, Cultivar 1 was grown on soils with significantly higher Zn, Cu and Mn EDTA concentration and Cultivar 2 on soils with high Fe EDTA concentration (Table 4). Investigated wheat genotypes achieved different yield (Table 5) and were used to produce the wholemeal, integral flour and to determine concentration of Fe, Mn, Zn, Cu, Pb, Cd (mgkg^{-1}) in flour. Therefore, the highest concentration in integral wheat flour was found for Fe, than lower concentrations for Mn, Zn, Cu, Pb and the lowest concentration was found for Cd. These results were found for all soil samples in average and for acid group of soil. On calcareous soil, the highest concentration in integral flour was found for Mn (Table 6). The highest variability of measured concentrations in integral flour was found for Pb and Cd and the lowest for Cu and Mn (Table 5).

Table 2. Average of total and plant available heavy metals concentrations (mgkg^{-1}) in acid, calcareous and all analysed soils in average

Heavy metals	Production area	Fe	Mn	Zn	Cu	Pb	Cd
Total content (aqua regia)	Acid soils (Ovčara)	25925*	71*	78	24.9†	24.6*	0.395
	Calcareous soils (Dalj)	25250†	595†	111	26.8*	18.3†	0.379
Plant available (EDTA)	Acid soils (Ovčara)	50.9*	34.2	1.63*	5.1*	3.02	0.037
	Calcareous soils (Dalj)	11.4†	34.2	1.09†	4.6†	2.64	0.030

*, †, statistically significant differences ($p \leq 0.05$) between heavy metal concentrations in columns

Table 3. Average of total heavy metals concentrations (mgkg^{-1}) in soils used for different wheat genotypes growing

wheat genotypes	Fe	Mn	Zn	Cu	Pb	Cd
Cultivar 1	25820*	761*	76	24.5†	23.7*	0.365†
Cultivar 2	26100*	671*	79	24.4†	21.4†	0.372†
Cultivar 3	25810*	666*	139	25.0†	20.4†	0.406*
Cultivar 4	24620†	515†	83	29.6*	20.4†	0.405*

*, †, statistically significant differences ($p \leq 0.05$) between heavy metal concentrations in columns

Table 4. Average of EDTA extracted (plant available) heavy metals concentrations (mgkg^{-1}) in soils used for different wheat genotypes growing

Wheat genotypes	Fe	Mn	Zn	Cu	Pb	Cd
Cultivar 1	32.35*†	37.30*	1.59*	5.1*	2.97*†	0.032
Cultivar 2	40.73*	39.37*	1.35*†	4.7†	2.65†	0.033
Cultivar 3	31.45†	40.75*	1.12†	4.5†	2.29†	0.029
Cultivar 4	20.04‡	19.36†	1.38*†	5.2*	3.42*	0.039

*, †, ‡, statistically significant differences (p ≤0.05) between heavy metal concentrations in columns

The wholegrain, integral flour derived from Cultivar 3 had the highest concentration of all analyzed heavy metals (Table 6). The Fe concentration was the highest concentration of analysed heavy metals in all genotypes excluding Cultivar 1 with highest Mn concentration. Also, the element with lowest concentration in Cultivar 1 flour was Pb, while other genotypes concentrated Cd in lowest concentrations. In flour of all genotypes Zn was third and Cu on the fourth place (Table 6).

Soil pH showed a significant influence to heavy metals grain concentration. Therefore, the lowest concentration of Pb was determined in integral flour derived from Cultivar 4 and the highest in Cultivar 2 and Cultivar 1 wholegrain flour. Also, concentration of Pb in integral flour derived from Cultivar 2 and Cultivar 4 had statistically significant lower concentrations of Pb on acid than on calcareous soils (Table 7). The highest concentration of Cd on acid soils was determined in integral flour of Cultivar 1. On calcareous soils the highest concentration of Cd was determined in Cultivar 3 grain and the lowest in Cultivar 2 grain (Table 7, Figure 1).

DISCUSSION

The results of this study have shown that the concentration of heavy metals in wheat grain was primarily related to properties of each genotype, the properties of soil on which certain genotype is grown, and total wheat yield.

Table 5. Genotypes grain yield and heavy metals concentration (in average on all soils) in integral flour of different wheat genotypes

Wheat genotypes	Grain yield	Heavy metal concentration (mgkg^{-1})					
	(tha^{-1})	Fe	Mn	Zn	Cu	Pb	Cd
Cultivar 1	7.60*	31.3†	35.0†	14.9‡	2.2§	0.030†	0.031*
Cultivar 2	6.35†	33.9†	32.6†	17.8†	2.8‡	0.132†	0.016†
Cultivar 3	4.50c	59.6*	50.9*	22.9*	4.1*	0.149*	0.035*
Cultivar 4	6.30†	36.7†	36.3†	17.1†‡	3.2†	0.094*†	0.014†

*, †, ‡, § statistically significant differences (p ≤0,05) between heavy metal concentrations in columns

Table 6. Average concentration of heavy metals in integral flour impacted by soil acidity (mgkg^{-1})

Soil	Fe	Mn	Zn	Cu	Pb	Cd
all soil types	40.4*	38.7*	18.2†	3.1‡	0.102‡	0.024‡
acid soil types	46.6*	34.4†	20.1‡	3.2§	0.047§	0.028§
calcareous soil types	33.9†	41.0*	16.2‡	2.9§	0.157¶	0.019¶

*, †, ‡, §, ¶ statistically significant differences (p ≤0,05) between heavy metal concentrations in rows

Grain yield is very important in terms of explaining the differences between the heavy metals concentration in plants parts including wheat grain mainly because of the dilution effect, since we expect that higher yield will result in lower concentration of heavy metals in plant parts and opposite. Increment of crop yield on limed acid soils leads to a significant decrease in the concentration of Mn from toxic to normal values in cereal grain (13). This fact is very important considering that the majority of wheat is used for bread production and bread is an important diet cereal product providing as much as 50-90 % of total caloric and protein intakes. The annual average consumption of bread and other bakery products in Croatia for 2009 was 74,2 kg per household

Table 7. Average concentrations of heavy metals in integral flour made by different wheat genotypes cropped on different soils (mgkg^{-1})

	Acid soil					
Wheat genotypes	Fe	Mn	Zn	Cu	Pb	Cd
Cultivar 1	33.6†	30.6†	16.4‡	2.3§	0.061*	0.0416
Cultivar 2	36.3†	27.7†	20.9†	3.1‡	0.061*	0.0205
Cultivar 3	76.9*	49.8*	24.5*	4.1*	0.041*	0.0367
Cultivar 4	40.5†	27.9†	18.5†‡	3.5†	0.023*	0.0138
	Calcareous soil					
Wheat genotypes	**Fe**	**Mn**	**Zn**	**Cu**	**Pb**	**Cd**
Cultivar 1	29.0†	39.4†‡	13.3‡	2.1§	0.02*†	0.023*†
Cultivar 2	21.5†	37.6‡	14.8†‡	2.5‡	0.203 *	0.011†
Cultivar 3	42.2*	52.0*	21.2*	4.1*	0.258*	0.033*
Cultivar 4	32.9†	43.0†	15.6†	3.0†	0.165 *†	0.013†

*, †, ‡, § statistically significant differences (p ≤0,05) between heavy metal concentrations in columns

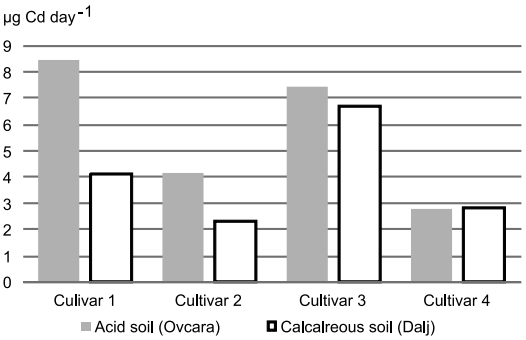


Figure 1. Soil and wheat genotype impact on potential daily Cd intake by integral flour bread

member, which is 203 g of bread consumed daily (14) (11). Integral flour derived from Cultivar 3 had the highest concentration of all heavy metals. We can assume that this was the effect of the yield level because Cultivar 3 had the lowest yield (4,5 t ha^{-1}), but other genotypes do not confirm this hypothesis because there is no statistically significant difference between the concentration of Fe and Mn in other three cultivars, although Cultivar 1 had significantly the highest yield (7,6 t ha^{-1}). Furthermore, Cultivar 4 (6,3 t ha^{-1} in average) was grown on soils with low concentration of available Fe and Mn, but concentration in integral flour was the same as for Cultivar 2 and Cultivar 1. This indicates that varietal differences of heavy metals intake and translocation resulting in different concentration of Fe and Mn in wheat grain. The concentration level of Zn and Cu in all samples of wheat grain was inversely proportionate to yield and Zn and Cu determined by EDTA. According to some authors, this could be result of genotype differences in ability to grow and yield well when the availability of the micronutrient is low (15,16). Winter cereals screening has shown significant genetic variation in Zn and Mn efficiency use, which indicates that selection for improved micronutrient efficiency is possible (17). When grown on soils with low micronutrient availability, efficient genotypes have a grater yield in comparison to inefficient ones (18). These genotypes also offer a potential for grain production for human consumption with higher concentration of Fe, Zn and Cu, the three micronutrients deficient for about a third of the world's population.

In our research, genotype diversity was the most obvious in concentrations of Pb and Cd. The transfer of Pb and Cd into wheat flour can be expected since about 61 % of all minerals in grain are contained in the aleuronic layer (19,20). The highest total concentration of Pb in this investigation was found in Cultivar 3 and the lowest in Cultivar 1 corresponding to lowest yield of Cultivar 3. Cd concentration in integral flour was not comparable to the yield level. This could be result of presence of other heavy metals in soil, because heavy metals may exert antagonistic, additive and/or synergetic effect on each other intake by plants (21). This interaction is most pronounced in Zn and Cd intake. However, Pb and Cd content in bread samples are valuable as general indicators of environmental pollution because highest uptake of Pb and Cd occurred during the heading-grain maturation period (22). The maximum allowable levels (MAL) of Cd and Pb in wheat flour in Croatia is 0,1 $mgkg^{-1}$ and 0,2 $mgkg^{-1}$ respectively (23), and all the average values of measured heavy metals concentrations were below MAL (23). Finally, we can say that large yield differences of the most grown Croatian wheat genotypes affect differently concentrations of essential heavy metals because the higher yield decreased concentrations of Fe, Mn, Zn and Cu. On the other hand, the impact of yield on the concentration of toxic heavy metals Pb and Cd was not observed, or not correlated with concentrations of total and available Pb and Cd, what could be direct result of genetic specificity and variability.

The soil properties and wheat genotype differences can very significantly impact daily cadmium and lead intake. If consumers in Croatia used daily 203 g of bread made by integral flour, they would intake 2.31 to 8.44 μg Cd daily, depending on soil and wheat genotype. The minimum daily intake can be compared as Cd average amount in two cigarettes (Cultivar 2 on calcareous soil), up to maximum of Cd average amount in eight cigarettes (Cultivar 1 on acid soil) (24,25). These possible intakes are very important since wheat has highest contribution of food to cadmium dietary intake (45% in Dutch) (26). Although Cultivar 1 produced highest grain yield, the highest Cd intake would be result of consumption of bread made by integral flour of Cultivar 1, slightly lower intake by Cultivar 3 on acid (7.45 μg Cd daily) and calcareous (6.70 μg Cd) soil than Cultivar 2 on acid and Cultivar 1 on calcareous soils (4.16 and 4.12 μg Cd, respectively). The lowest Cd intake would be from consuming bread made of Cultivar 4 regardless to soil (2,8 μg Cd) and Cultivar 2 on calcareous soils (2,31 μg Cd daily). The soil impact on potential Cd daily intake would be also significant, since bread originated from cropping on acid soil would result in higher amount of Cd daily intake than from cropping on calcareous soils (5,71 vs. 3,99 μg Cd).

The potential daily intake of lead by consuming bread made from analysed integral flour would be on acid soils lowest by cropping Cultivar 4

(4,67 μg Pb daily) and highest by Cultivar 3 and Cultivar 1 (12,55 and 12,40 μg Pb daily, respectively). The cropping on calcareous soil on locality Dalj would result in a higher lead intake than on acid soil on the locality of Ovcara.

The highest average intake of all four elements would be using flour of Cultivar 3, and lowest using Cultivar 1 or Cultivar 2.

The analysed soil and winter wheat genotypes have significant impact on potential daily intake of toxic and essential heavy metals by integral flour or bread.

FUNDING

This work was supported by the Croatian Food Agency, Croatia, research project "Toxic and essential heavy metals in wheat grain on Croatian acid and calcareous soils".

TRANSPARENCY DECLARATIONS

The wheat genotypes in this study were selected by the criterion of quality and standard representing in agricultural production Croatian.

REFERENCES

1. Imtiaz M, Rashid A, Khan P, Memon MJ, Aslam M. The role of micronutrients in crop production and human health. Pak J Bot 2010; 42:2565-78.
2. Demment MW, Young MM, Senseing RL. Providing Micronutrients trough Food-Based Solutions: A Key to human and National Development. ASN J Nutr 2003; 133:3879S-85S.
3. Khaniki JGHR, Deghani MH, Mahvi AM, Nazmara S. Determination of trace metal contaminants in Edible Salts in Teheran (Iran) by atomic absorption spectrophotometry. J Biol Sci 2007; 5:811-4.
4. Khaniki JGHR, Vaezi F, Yunesian M, Nabizadeh R, Paseban GHA. Detection of baking soda in flat bread by direct pH metery and alkalinity measurement. J Applied Sci 2007; 7:3584-7.
5. Fu J, Zhou Q, Liu J, Liu W, Wang T, Zhang Q, Jiang G. High levels of heavy metals in rice (Oryza sativa L) from a typical E-waste recycling area in southeast China and its potential risk to human health. Chemosphere 2008; 71:1269-75.
6. Tang X, Shen C, Shi D, Cheema SA, Khan MI, Zhang C, Chen Y. Heavy metal and persistent organic compound contamination in soil from Wenling: An emerging e-waste recycling city in Taizhou area, China. J Hazard Mater 2010; 173:653-60.
7. Hooda PS, Alloway BJ. The effect of liming on heavy metal concentrations in wheat, carrots and spinach grown on previously sludge-applied soils. J Agr Sci 2009; 127:289-94.
8. Khoshgoftarmanesh AH, Schulin R, Chaney RL, Daneshbakhsh B. Micronutrient-efficient genotypes for crop yield and nutritional quality review. Agon Sustain Dev 2010; 30:83-107.
9. International Organization for Standardization. ISO 11466: Soil quality – Extraction of trace elements soluble in aqua regia. Genève, 1994.
10. Trierweler FJ, Lindsay WL. EDTA-ammonium carbonate test for Zn. Soil Sci Soc Amer Proc 1969; 33:49-54.
11. International Organization for Standardization. ISO 10390: Soil quality – determination of pH. Genève, 1994.
12. Kingston HM, Jassie LB. Microwave Energy for Acid Decomposition at Elevated Temperatures and Pressures Using Biological and Botanical Samples. Anal Chem 1986; 58:2534.
13. Kovačević V, Rastija M. Impacts of liming by dolomite on the maize and barley grain yields. Poljoprivreda 2010; 2:3-8.
14. Croatian bureau of Statistic. Croatian Statistical Yearbook. Zagreb: CBS, 2009.
15. Liu J, Li K, Xu Jiakuan, Liang J, Lu X, Yang J, Zhu Q. Interaction of Cd and five mineral nutrients for uptake and accumulation in different rice cultivars and genotypes. Field Crop Res 2003; 83:271-81.
16. Welch RM, Graham RD. Breeding for micronutrients in staple food crops from a human nutrition perspective. J Exp Bot 2004; 396:353-64.
17. Imtiaz M, Alloway BJ, Aslam M, Memon MJ, Khan P, Siddiqui SH, Shah KH. Zinc sorption in selected soils. Comm Soil Sci Plant Anal 2006; 11-12: 1675-88.
18. Imtiaz M, Alloway BJ, Khan P, Memon MJ, Siddiqui SH, Aslam M, Shah KH. Zinc deficiency in selected cultivars of wheat and barley as tested in solution culture. Comm Soil Sci Plant Anal 2006; 11-12: 1703-21.
19. Zhang J, Du K, Chen G, Wang Y, Zhou W, Sun G. Distribution of Pb in different parts of wheat grains and its relationship with other 8 elements. In: Proceedings of The 4th International Conference on Bioinformatics and Biomedical Engineering (iCBBE 2010), Chengdu, China, June 18-20, 2010. Article 5515239, pp.: 1-4. IEEE Xplore Digital Library. http.//ieexplore.ieee.org/xpl/freeabs_all.jsp?arnumber=5515239.
20. Fan MS, Zhao FJ, Fairweather-Tait SJ, Poulton PR, Dunham SJ, McGrath SP. Evidence of decreasing mineral density in wheat grain over the last 160 years. J Trace Elem Med Biol 2008; 22:315-24.
21. Luo Y, Rimmer DL. Zinc–copper interactions affecting plant growth on metal-contaminated soil. Environ Pollut 1995; 88:79-83.
22. Awaad HA, Youssef MAH, Moustafa ESA. Identigication of Genetic Variation among Bread Wheat Genotypes for Lead Tolerance Using morpho-physiological and molecural markers. Am J Sci 2010; 10:1142-53.
23. Ministry of Health and Social Welfare of The Republic of Croatia. Regulation of toxins, metals, metalloids and other harmful substances that may be present in food. Narodne novine 16, 2005.

24. Watanabe T., Kasahara M., Nakatsuka H., Ikeda M. Cadmium and lead contents of cigarettes produced in various areas of the world. Scie Total Environ 1987, 66:29-37.
25. Galazyn-Sidorczuk M, Brzóska MM, Moniuszko-Jakonium J. Estimation of Polish cigarettes contamination with cadmium and lead, and exposure to these metals via smoking. Environ Monit Assess 2008, 137:481-93.
26. Winter-Sorkina R., Bakker MI, Donkersgoed G., Klaveren JD. Dietary intake of heavy metals (cadmium, lead and mercury) by the Dutch population. Bilthoven, Netherlands: National Institute of Public Health and the Environment (RIVM), 2003; RIVM report 320102001.

Utjecaj kemijskih svojstava tla i sorte pšenice na sadržaj mikroelemenata i toksičnih elemenata u integralnom brašnu

Zdenko Lončarić[1], Brigita Popović[1], Krunoslav Karalić[1], Zorica Jurković[2], Ante Nevistić[3], Meri Engler[1]

[1]Sveučilište ž'Josip Juraj Strossmayer'', Poljoprivredni fakultet u Osijeku, Osijek; [2]Hrvatska agencija za hranu, Osijek; [3]Inspecto d. d., Đ akovo; Hrvatska

SAŽETAK

Cilj Istražiti utjecaj kemijskih svojstava tla i različitih sorata pšenice na usvajanje i translokaciju teških metala u integralno brašno pšenice.

Metode Uzorci tla prikupljeni su s dva različita proizvodna područja u Republici Hrvatskoj: Dalj i Ovčara. Osim uzoraka tla, prikupljeni su i uzorci zrna četiriju najzastupljenijih hrvatskih sorata pšenice. Ukupno je prikupljeno i analizirano 40 uzoraka tla i 40 uzoraka zrna, u kojima je određena koncentracija ukupnih (zlatotopka) i biljci pristupačnih (EDTA) teških metala Fe, Mn, Zn, Cu, Pb, Cd.

Rezultati Na proizvodnom području Ovčara pH_{KCl} kretao se od 5,63 do 6,25, dok je pH_{KCl} na proizvodnom području Dalj bio od 6,95 do 7,37. Najveće ukupne koncentracije teških metala u tlu utvrđene su za Fe, zatim slijede Mn, Zn, Cu, Pb, dok je najnižu koncentraciju imao Cd. Najveće koncentracije pristupačnih teških metala u tlu utvrđene su za Mn, zatim slijede Fe, Cu, Pb, a najnižu biljci pristupačnu koncentraciju imao je Cd. U integralnom brašnu pšenice zabilježena je najviša koncentracija Fe, nešto niža Mn, Zn, Cu, Pb, dok je najniža opet bila koncentracija Cd. Dakle, ukoliko potrošači u Republici Hrvatskoj dnevno konzumiraju 203 g integralnog brašna, unijet će u organizam od 2,31 do 8,44 μg Cd dnevno, što prvenstveno ovisi o sorti pšenice i svojstvima tla.

Zaključak Analizirana svojstva tla i pojedine sorte pšenice imaju značajan utjecaj na potencijalno dnevno unošenje toksičnih i esencijalnih teških metala putem integralnog brašna.

Ključne riječi teški metali, tlo, sorte pšenice, integralno brašno

NOTES

Risk factors and diabetic retinopathy

Admira Dizdarević[1], Amila Alikadić-Husović[2], Vahid Jusufović[3]

[1]Department of Ophthamology, Cantonal Hospital Zenica, [2]Ophthamology Clinic, University Clinical Center of Sarajevo, [3]Ophthamology Clinic, University Clinical Center Tuzla; Bosnia and Herzegovina

Corresponding author: Admira Dizdarević; Department of Ophtamology, Cantonal Hospital Zenica; Crkvice 67, 72000 Zenica, Bosnia and Herzegovina; Phone: +387 32 227 332 ; fax: +387 32 226 998; E-mail: ad25801@yahoo.com

Original submission: 26 March 2011; **Revised submission**: 29 April 2011; **Accepted**: 28 July 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):104-106

ABSTRACT

The aim of the study was to determine the correlation between risk factors and diabetic retinopathy, which is the leading cause of blindness in developed countries for patients aged 20 to 65. We compared risk factors between patients without retinopathy, with non-proliferate and with proliferate retinopathy ($p< 0.05$). Duration of diabetes is most important for the development of retinopathy. Hyperglycaemia and high blood pressure are important for progression. Better control of blood sugar and elevated blood pressure can reduce progression of retinopathy and risk of vision loss.

Key words: diabetic retinopathy, risk factors, progression

INTRODUCTION

Diabetic retinopathy is a chronic, microvascular complication of diabetes. A long-lasting diabetes and initial preserved visual activity give false security and explain devastating findings in many diabetics (26-36%) who have never been examined by an ophthalmologist (1,2). Except the duration of diabetes, bad metabolic control, arterial hypertension, smoking, obesity, hyperlipidemia are notable for the development and progression of retinopathy (2-4). Pregnancy is occasionally accompanied by quick progression of retinopathy (2). If nephropathy has been developed, it is accompanied by the progression of retinopathy (3,4).

The most frequent cause of reduced visual activity by diabetic retinopathy is macular edema, which can occur in all three clinical forms of retinopathy (non-proliferate, pre-proliferate and proliferate) (2,5). The best insight to the state of disease gives fundus examination: ophthalmoscopy, fundus photography, OCT, fluorescein angiography (6,7).

The aim of this study was to analyze the duration of diabetes mellitus, values of HbA1C, cholesterol and triglycerides in blood, arterial tensions by respondents with proliferate, non-proliferate retinopathy and diabetics without retinopathy.

PATIENTS AND METHODS

In this retrospective, comparative and descriptive study risk factors for the diabetic retinopathy were analyzed by randomly selected samples including 30 patients with proliferate diabetic retinopathy, 30 patients with non-proliferate retinopathy and 30 patients with diabetes but without diabetic retinopathy. All patients were hospitalized at the Department for Internal Diseases of the Cantonal Hospital of Zenica during 2007, and prepared by ophthalmoscopy.

An eye with higher level of retinopathy was examined. Existence of arterial hypertension, values of HbA1C, level of cholesterol and triglycerides in blood were used from patients' history records.

Patients with non visible front segment of eye and other vascular retinal diseases were excluded from this study.

Kolmogorov-Smirnov test was used for testing significant difference at the level of $p<0.05$.

RESULTS

Duration of diabetes has proven to be the most important factor in a very early stage of diabetic retinopathy ($p<0.001$). The value of lipids showed

Table 1. Kolmogorov-Smirnov test between patient groups

	Patient group Mean value			p (between the groups)		
Variable	I	II	III	I-II	I-III	II-III
Duration (years)	4.8333	12.7667	16.1333	P<.001	p<.001	p>.10
HbA1C (‰)	8.9033	9.3400	10.0800	p>.10	p<.025	p<.025
Systolic pressure (mm/Hg)	132.8333	144.1667	153.333	p>.10	p<.05	p>.10
Diastolic pressure (mm/Hg)	83.3333	88.1667	92.000	p>.10	p<.05	p>.10
Cholesterol (mmol/L)	5.2033	5.0367	5.7867	p>.10	p>.10	p<.10
Triglycerides (mmol/L)	1.9167	2.0067	2.1967	p>.10	p>.10	p>.10

no statistically significant difference between the patients without retinopathy and with proliferate retinopathy ($p>0.1$). A very significant difference was noted in values of HbA1C ($p<0.025$) between the group with non-proliferate and the group with proliferate form of retinopathy (Table 1).

DISCUSSION

The severity of diabetic retinopathy is best shown when it is related to blindness that diminishes the quality of life, and it is a great burden for national funds. Around 2% of the total population with diabetes is blind, which is ten times more than in the general population (2).

Diabetic retinopathy is rarely developed within five years since the beginning of disease or before puberty (1,2). Around 5% of type 2 diabetics had already had diabetic retinopathy during the first examination (1,2,3). After 20 years of diseases almost all patients with type 1 and more than 60% of those with type 2 diabetes mellitus show a certain degree of diabetic retinopathy (1,2). Lack of a significant difference in the duration of the disease between groups (12.76 and 16.13 years) in this investigation could be explained by late diagnosis of diabetes among patients with proliferative form of the disease (4).

The American Diabetes Association has proposed that all diabetics (insulin dependent and insulin independent) should strive to have values of HbA1C less than 7.0% in order to prevent and reduce complications of diabetes, including diabetic retinopathy (2). In all three groups of patients investigated in this study perceived values of HbA1C were more than 7%, and it can be explained by the fact that all patients were mostly hospitalized because of the bad metabolic control. An English prospective diabetic study has shown a relation between blood sugar level and risk of microvascular complications where each decreased percent of HbA1C for 1% led to up to 35% reduction risk of microvascular complications (4).

This study has proven a significant difference ($p<0.05$) in the values of systolic and diastolic pressure between the two groups. Poor control of arterial hypertension in cases of type 1 and type 2 diabetes is accompanied by worsening of retinopathy and development of proliferate retinopathy (4,8,9). Early and adequate control of arterial hypertension has a very favorable effect on the state of edema maculae and retinopathy generally (8,9,10).

A relation between the level of serum lipids and retinopathy has been investigated in many studies (11). Some studies have shown a positive relation between cholesterol and existence of solid exudates (11), and other studies have shown importance of triglycerides in progression of retinopathy (11). There were studies that have not proved the relation between serum lipids and diabetic retinopathy (11), similar to the results of this study.

In conclusion, duration of diabetes is the most important risk factor for the development of diabetic retinopathy because poorly regulated blood sugar level and arterial hypertension influence the gravity of diabetic retinopathy and its progression. As retinopathy is developed after long duration of diabetes, early detection, monitoring and intensive metabolic control are needed to prevent the progression of diabetic retinopathy and vision loss.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Kanski JJ. Klinička oftalmologija. Beograd: Data Status, 2004:439-55.
2. Donald S, George L. Diabetic retinopathy. Diabetes Care 2003; 26:99-102.
3. Ossama H. Prevalence and risk factors for diabetic retinopathy among Omani diabetics. Br J Ophthalmol 1998; 82:901-6.
4. The Diabetes Control and Complications Trial Research Group. The effects of intensive tretment of diabetes on the development and progession of long-term complication in Insulin-Dependent Diabetes mellitus. N Engl J Med 1993; 329: 977-86.
5. Fine BS, Brucker AJ. Macular edema and cystoid macular edema. Am J Ophthalmol 1981; 92: 466-81.
6. Early Treatment Diabetic Retinopathy Study Reserch Group. Study Report Number 11. Classification of diabetic retinopathy from fluorescein angiograms. Ophthalmology 1991; 98: 807-22.
7. Massin P. Girach A. Erginay A. Gaudric A. Optical coherence tomography: a key to the future management of patients with diabetic macular oedema. Acta Ophthalmol Scand 2006; 84:466-74.
8. Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM. Risks of progression of retinopathy and vision loss related to high blood pressure control in type 2 diabetes mellitus. Arch Ophthalmol 2004; 122:1631-40.
9. Matthews DR, Stratton IM, Aldington SJ, Holman RR, Kohner EM, UK Prospective Diabetes Study Group. Risks of progression of retinopathy and vision loss related to high blood pressure control in type 2 diabetes mullitus. Arch Ophthalmol 2004; 122:1631-40.

10. Stefansson E. Prevention of diabetic blindness. Br J Ophthalmol 2006; 90:2-3.
11. Su DH, Veo KT. Diabetic retinopathy and serum lipids. Singapore Med J 2000; 41:295-7.

Faktori rizika i dijabetična retinopatija

Admira Dizdarević[1], Amila Alikadić-Husović[2], Vahid Jusufović[3]

[1]Služba za očne bolesti, Kantonalna bolnica Zenica, [2]Očna klinika, Klinički centar Univerziteta u Sarajevu, [3]Očna klinika, Univerzitetski klinički centar Tuzla; Bosna i Hercegovina

SAŽETAK

Cilj rada je analizirati faktore rizika za nastanak dijabetične retinopatije koja je vodeći uzrok gubitka vida u razvijenim zemljama, kod pacijenata u dobi od 20 do 65 godina. Uspoređene su srednje vrijednosti faktora rizika kod dijabetičara bez retinopatije, s neproliferativnom i s proliferativnom retinopatijom ($p<0.05$). Dužina trajanja dijabetesa najznačajnija je u nastanku, a hiperglikemija i arterijska hipertenzija u progresiji retinopatije, što je u skladu s podacima iz literature. Regulacijom hiperglikemije i arterijske hipertenzije moguće je reducirati progresiju retinopatije i rizik od gubitka vida.

Ključne riječi: dijabetična retinopatija, faktori rizika, progresija

NOTES

Cyclocryotherapy in neovascular glaucoma treatment

Mirjana A. Janićijević-Petrović[1], Tatjana Šarenac[1], Marko Petrović[2], Dejan Vulović[2], Katarina Janićijević[2]

[1]Clinic of Ophthalmology, Clinical Centre of Kragujevac, [2]Medical Faculty, University of Kragujevac, Serbia

Corresponding author: Mirjana A. Janićijević-Petrović; Clinic of Ophthalmology, Clinical Centre Kragujevac, Kneza Miloša 3/1, 34000 Kragujevac, Serbia; Phone: +381 34 369 828; fax.: +381 34 370 037; E-mail: mira.andreja@yahoo.com

Original submission: 29 April 2011; **Revised submission:** 29 August 2011; **Accepted**: 30 November 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):106-109

ABSTRACT

The main goal in the struggle with neovascular glaucoma is to control intraocular pressure (IOP) and pain. 152 patients, e.g., 203 eyes, were examined at the Clinic of Ophthalmology, Clinical Centre of Kragujevac, Serbia, in period between 01. 01. 2005 - 31. 12. 2010. Cyclocryoanemisatio was performed for all patients. Measurments of IOP showed statistical significant changes before and after the treatment for every patients. There was no difference in sex distribution, but a difference was noted in age distribution. Early posttreatment complications included hyphema, fibrin's exudation, chemosis. Cyclocryotherapy is usefull and accessible method for control of intensive pain in neovascular glaucoma.

Key words: neovascular glaucoma, cyclocryotherapy, pain.

INTRODUCTION

Neovascular glaucoma (NVG) is the most frequent type of secondary glaucoma (1). The main cause for the neovascular glaucoma is fibrous membrane with new blood vessels over the iridocorneal angle. The most frequent cause of NVG is central retinal vein occlusion (CRVO) (36%), proliferative diabetic retinopathy (32%), and carotid or central retinal artery obstructive diseases; rarely tumours, injuries or inflammation of the choroideae, etc. (2). Neovascular signs are described at 80% of patients in the first 6 months from appearing of the ischemic form of CRVO, and in 15% with non ischemic form (3,4). Treatment of the early stage is: prophylaxis - control of the patients with occlusive syndromes, diabetic retinopathy; prevention - retinal laserphotocoagulation; medical therapy - beta adrenergic blockers, carbonic anhydrase inhibitors, prostaglandins, mydriatics, steroids and symptomatically osmotherapy (1-3). The modern aspect of the treatment is intravitreal or intracameral application of anti-VEGF, in the early stage of NVG (3,4). The other modern treatment methods are: cyclodestructive methods, Neodmium:Yag transscleral cyclophotocoagulation, retrobulb, as well as surgical procedures, trabeculectomy with antifibrotic agents and valve implants surgery (5-7). Cyclocryoanemisatio is a surgical method *ab externo* (8, 9). By fibrosing ciliary processes with cryo-probe, decreased production of the humor aqueous and intraocular pressure (IOP) can be achieved. The complications of this procedure are: hypotony, phthisis, retinal detachment, hyphema, iritis, cataract, macular edema, etc (11). The most difficult complications include sympathetic ophthalmia and anterior segment ischemia (11).

The aim of our study was to investigate and signify the efficacy of cyclocryotherapy in patients with NVG and intensive ocular pain.

PATIENTS AND METHODS

The retrospective study included 203 eyes or 152 patients in the Clinic of Ophthalmology, Clinical Centre of Kragujevac in Kragujevac, Serbia, in the period from 01. 01. 2005 to 31. 12. 2010. Cyclodestructive procedure was done in aseptic conditions, with parabulbar anaesthesia and proper technical conditions - temperature, pressure and time (with Cryo-Line apparatus made by Opticon, Italy, 2000). It used 10-15 cryo applications, with maximum possible cryo-probe diameter, at almost whole *pars plana* for 99 seconds per application and with temperature over - 60 °C. A standard clinical protocol for the glaucomatous patients in preoperative and postoperative period was used. The pain control is a subjective symptom of patients with neovacular glaucoma, and there were no standard levels for its measuring. The statistical program SPSS, version 13 (x^2 test), and $p<0.01$ was used.

RESULTS

A total number of 152 patients was examined, of which 80 (52.63%) were female (p=0.516). Most patients were in the age between 51 - 60 years (p<0.01). All patients were over thirty years of age, and the fewest patients were at the age between 81 - 90 years. There was no significant genetic predisposition, but with statistical difference by family predisposition (p<0.01). Diabetic retinopathy was found in 113 (55.67 %), and occlusive syndrome in 58 (28.57 %) patients, absolute glaucoma in 54 (26.6%), postuveitical glaucoma in 38 (18.72%), posttraumatic glaucoma in 22 (10.84%) and postsurgical glaucoma in 20 (9.85%) patients, (p<0.01). Cryo-probes were done at the whole circumferential in 119 (58.62%) eyes (p<0.01), followed by 64 (31.52%) patients when we used 270°, and some at 180° (20/203-9.85%). A significant decrease of intraocular pressure (IOP) was noted in the range of 40 mm Hg +/- 21 mm Hg to 21 +/- 7.1 mm Hg (p<0.01 before and after the treatment). Correlation of the intraocular pressure before and after the treatment has shown a decreasing trend in all categories (p<0.01) (Table1). The optimal IOP pressure was achieved in the next 6 - 10 months after the treatment, without intensive ocular pain.

Table 1. Number of patients and intraocular pressure values before and after the treatment

	Number (%) of patients with intraocular pressure (mmHg)					
	10- 20	21-30	31-40	41- 50	51-60	61-70
Before treatment	0	7 (3.45%)	101 (49.75%)	39 (19.21%)	21 (10.34%)	35 (17.24%)
After treatment	0	147 (72.41%)	39 (19.21%)	13 (6.40%)	2 (0.98%)	2 (0.98%)

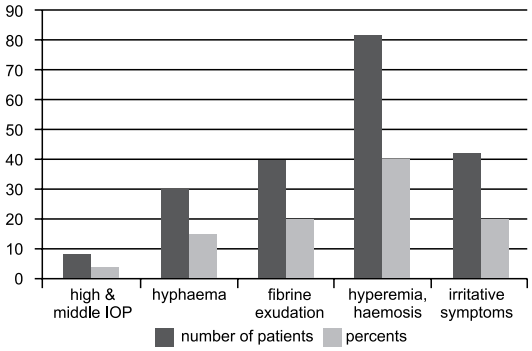


Figure 2. Cyclotherapy complications in patients with neovascular glaucoma

It ensured better quality of life for the patients. During the investigation some complications were found after this procedure such as: insufficient decrease of IOP in 8 (3.94%) eyes, hyphema in 30 (14.78 %), fibrin's exudation in 40 (19.7 %), conjunctival chemosis in 81 (39.9%) and irritative symptoms in 42 (20.69%) (p<0.01), (Figure 2). The optimal IOP without extreme hypotonia was found in 119 (58.62%) eyes. Adjuvant medical therapy was used in 71 (34.98%) eyes. Reintervention was performed in 6 (3.95%) cases, and combination of reintervention and medical therapy in 4 (2.63%) patients. (p<0.01). In patients who used only medicament therapy there was no significant statistical difference of achieved intraocular pressure.

DISCUSSION

The results of this study have not shown statistical difference in gender of patients with neovascular glaucoma as well as age distribution. However,, with regard to the age, most patients were older (51 - 60 years of age), which is in concordance with the results of other recent studies (3,4). Genetic predisposition has not been important for our patients, as it was shown in other studies (3). All available data indicated diabetic retinopathy (36%) and occlusive syndrome (32%) as main causes for neovasular glaucoma as in our study. According to the studies in last twenty years, we can see that cyclocryotherapy reduces IOP for 30mmHg in 73% cases in the period of about twelve months, which is in positive correlation with the results of our study (5). Reintervetnion was indicated in 7.9% of our cases, with adjuvant medical therapy which is relevant for most of the available data (7, 8). Lowering of the

IOP was not succesfull in 3.95% of our patients, comparing with 8% in other studies (5, 10). Postoperatively, transient hyphema was presented in 14.78% of our patients, and it is in correlation with 23% from literatures (11), but both irritative symptoms and fibrin exudation were not in correlation according to available data (11, 12). We did not note complications like phthisys or extreme hypotony, but it was described in some research up to 8% (10, 13).

The modern concept of NVG treatment includes the medicament therapy at the first stage of the disease and surgical therapy at the later stage. Medicament antiglaucomatous therapy is affordable in all countries, so there are no socio-economic problems for providing the medicines (8). The efficiency of medical treatment is evident in lowering of the intraocular pressure for 30% (6,8). In the late stage of NVG when it could not reach optimal intraocular pressure by medical therapy, intravitreal or intracameral anti-VEGF therapy or trabeculectomy with the antifibrotic agents were suggested (6,8). This kind of treatment is very expensive for majority of countries, especially for developing countries, such as Serbia (8). Filtrating operations with valve implants are indicated for the patients with useful visual acuity and high intraocular pressure value (6,7,8).

However,, what shall we do with painful and blind eye? We suggest that explanation for our results can be attributed to technical conditions of used equipment, like reachable temperatures, time of application, and diameter of cryoprobe. In our opinion, the great importance is in recognizing individual aspects of the painful eye and the patient's condition in order to perform optimal therapy. It is imperative for ophthalmologist to preserve the anatomical integrity of every blind eye. The postoperative complications should be treated by conservative approach, when we expect good results (12, 13). The great importance of this treatment modality in the struggle against great eye pain, both for the patient and ophthalmologist, is to be very patient.

Cyclocryotherapy is useful and accessible method for control of intensive ocular pain in patients with neovascular glaucoma. In the era of modern therapy, cyclocryotherapy is useful, but very expansive, so ophthalmologists must find optimal treatment for the patients. When there are no other effective and accessible solutions, and when ophthalmologists try to save the anatomy of blind eye, cyclocryotherapy is, in our opinion, an elegant treatment for the pain control. We must be reminded that sometimes we can use affordable, well known, simple and effective method of treatment.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Jack J Kanski. Ophthalmology. Belgrade: Data status, 2006:233-6.
2. Vancea PP, Abu-Taleb A. Current trends in neovascular glaucoma treatment. Rev Med Chir Soc Med Nat Iasi 2005; 109:264-9.
3. E-Medicine. Glaucoma neovascular. http://www.emedicine.com (10th March 2011).
4. Holló G. Diabetic neovascularisation and secondary glaucoma. Orv Hetil 2011; 152:1167-70.
5. Topozius F, Yu F, Coleman AL. Factors associeted with elevated rates of adverse outcomes after cyclodestructive procedures versus drainage device procedures. Ophthalmology 1998; 105:2276-81.
6. Alkawas AA, Shahien EA, Hussein AM. Menagnemt of neovascluar glaucoma with panretinal photocoagulation, intravitreal bevacizumab, and subsequent trabeculectomy with mitomycin C. J glaucoma 2010; 19:622-6.
7. Marey MH, Ellakwa FA. Intravitreal bevacizumab with or without mitomycin C trabeculectomy in the treatment of neovascular glaucoma. Clin Ophthalmol 2011; 5:841– 84.
8. Wasik A, Song HF, Grimes A, Engelke C, Thomas A. Bevacizumab in conjunction with panretinal photocoagulation for neovascular glaucoma. Optometry 2009; 80:243-8.
9. Jeon S, Lee NY, Park CK. Neovascuarl glaucoma following stereotactic radiosurgery for an optic nerve glioma: a case report. Korean J Ophthalmol 2010; 24:384-5.
10. Heuring AH, Hütz WW, Hoffman PC, Eckhardt HB. Cyclocryotherapy in neovascular glaucoma and non neovascular glaucoma, Klin Monatsbl Augenheilkd 1998; 213:213-9.
11. Vest E, Rong-Guang W, Raitta C. Transillumination guided cyclocryotherapy in the treatment of secondary glaucoma. Eur J Ophthalmol 1992; 2:190-5.
12. Shukia M, Thakkur N. A comparative evaluation of cyclocryotherapy, cyclodiathermy and cycloanemisatio in glaucoma. Indian J Ophthalmol 1981; 29:13-7.
13. Goldenberg-Cohen N, Bahar I, Ostashinski M, Lusky M, Weinberger D, Gaton DD. Cyclocryotherapy versus transscleral diode laser cyclophotocoagulation for uncontrolled intraocular pressure. Ophthalmic Surg Lasers Imaging 2005; 36:272-9.

Ciklokrioterapija u lečenju bolesnika s neovaskularnim glaukomom

Mirjana A. Janićijević-Petrović[1], Tatjana Šarenac[1], Marko Petrović[2], Dejan Vulović[2], Katarina Janićijević[2]

[1]Klinika za oftalmologiju, Klinički centar Kragujevac; [2]Medicinski fakultet Univerziteta u Kragujevcu; Srbija

SAŽETAK

Borba s neovaskularnim glaukomom je teška i neizvesna u smislu smanjenja intraokularnog pritiska (IOP) i bola. U ovo istraživanje bila su uključena 152 bolesnika, 203 očiju, lečenih na Klinici za oftalmologiju KC-a Kragujevac u Srbiji, u periodu od 01. 01. 2005. do 31. 12. 2010. godine. Kod svih bolesnika urađena je ciklokrioanemizacija u aseptičnim uslovima. Izmerene vrednosti IOP-a, pre i posle ciklokrioanemizacije, ukazivale su na značajne razlike; zabilježen je pad IOP-a kod svakog bolesnika, nezavisno od pola, ali ovisno od starosti pacijenta. Rane, postoperativne komplikacije bile su hifema, fibrinska eksudacija i hemoza. Ciklokrioanemizacija je korisna i dostupna metoda kontrole bola kod bolesnika s neovaskularnim glaukomom.

Ključne riječi: neovaskularni glaukom, ciklokrioanemizacija, kontrola bola

NOTES

Increasing incidence of rubella in Republika Srpska in the period 2006-2010

Veljko Ćejić[1], Tamara Naumović[2]

[1]City Institute for Public Health, [2]Institute of Medical Statistics and Informatics, School of Medicine, University of Belgrade; Beograd, Serbia

Corresponding author:

Tamara Naumović; Institute of Medical Statistics and Informatics, School of Medicine, University of Belgrade; Dr Subotica 15, 11 000 Beograd, Serbia; Phone: +381 11 2681 964; fax: +381 11 2659 533; E-mail: tamaranaumovic@yahoo.com

Original submission: 23 May 2011; **Revised submission**: 02 July 2011; **Accepted**: 02 July 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):109-111

ABSTRACT

The aim of this study was to investigate the incidence rate of rubella in Republika Srpska in the period between 2006 and 2010. The total number of 1236 cases of rubella was reported during the reporting period with manifold increasing incidence from 0.5 in 2006 to 54.7 in 2010 per 100,000 habitants. In the last two years of observation there was a disease outbreak in Republika Srpska. Inadequate immunization, migration and lack of funds caused a reduction in the overall level of public health and health system which led to a drastic increase in the number of rubella cases.

Key words: rubella, incidence, immunization

INTRODUCTION

Before the introduction of immunization (1969), in the United States (US) the epidemics of rubella occurred every 6-9 years. In the period 1962-1965 12,5 million cases of rubella were recorded in the US, resulting in 2000 cases of encephalitis, 11,250 fetal and 2100 infant deaths, and 20000 infants born with congenital rubella syndrome (CRS). At the time the costs were estimated at 1.5 billion dollars (1). According to the Center for Disease Control and Prevention (CDC) in 2001 in the US there were only 23 cases of rubella, 18 in 2002, and only 7 cases in 2003, and none was diagnosed in 2004 (1).

Immunization program to prevent rubella in Europe started in the seventies of the last century with selective vaccination of young girls aged 19, and later the mass vaccination of infants in most countries (2), and today the combined MMR vaccine (measles, mumps, rubella) is included in the mandatory immunization programs of most European countries. The aim of the vaccination was to suppress the transmission and primary morbidity of rubella and prevent the emergence of the CRS (3,4).

According to data of the World Health Organization from 2008 the largest number of rubella cases was recorded in Kazakhstan, Russia and in the United Arab Emirates (5). According to data for Serbia from 2009, 27 outbreaks of rubella were reported, with incidence rate of 0.37, and MMR vaccination achieved coverage and revaccination of 95% (6). Immunization preventing rubella in Bosnia and Herzegovina has been applying the combined MMR vaccine since 1980.

The aim of this study was to investigate the incidence of rubella in Republika Srpska in the period between 2006 and 2010, and to show the importance of complete vaccination (with two doses of MMR vaccine) against rubella in the population. Until now, there were no similar investigations in Republika Srpska.

PATIENTS AND METHODS

This is a descriptive epidemiological study which included all reported cases of patients suffering from rubella in the period from 2006 to 2010 in the territory of Republika Srpska. All demographic data, as well as data of gender, age, place of residence were collected from the records of the Institute of Public Health of Republika Srpska, Banja Luka, and from the services responsible for monitoring infectious diseases in some Health Centers in Republika Srpska. These institutions cover around 1 500 000 inhabitants. Rates were calculated based on the number of habitants according to the Census in 2006 and are expressed per 100.000 population. Linear regression analysis was used to calculate the incidence trend. The p values less than 0.05 were considered to be significant.

RESULTS

In Republika Srpska 1236 cases of rubella were recorded in the period 2006-2010. Incidence rates were low in the period from 2006 to 2008, but in 2009 and 2010 they occur much more frequently.

The disease mainly occurred sporadically - seven cases in 2006, three cases in each 2007 and 2008, resulting in the incidence of 0.5 and 0.2/100.000, respectively. During 2009 and 2010 17 rubella outbreaks were noted, with 1223 (around 99% of all) cases recorded in the five-year period. In 2010 11 outbreaks of rubella were registered with 766 (62% of all) cases (Table 1). No person had congenital rubella syndrome (CRS) and there were no death cases.

The geographical distribution of rubella cases has shown that the epidemics had mostly spread in eastern part of Republika Srpska. It was noted that the territory of Trebinje was the most affected area in the observed period. In 2010 a drastic increase of the rubella cases has been noted in East Sarajevo (Table 2).

Table 1. Epidemiological characteristics of rubella infections in Republika Srpska in the period 2006 - 2010

Year	No (%) of sporadic cases	No (%) of outbreaks	No (%) of cases in outbreak	Incidence (per 100 000)	% of participation in respiratory diseases
2006	7 (0.6)	0	0	0.5	0.09
2007	3 (0.2)	0	0	0.2	0.02
2008	3 (0.2)	0	0	0.2	0.03
2009	0(0)	6 (35)	457(37.4)	32.6	3.31
2010	0(0)	11(65)	766(62.6)	54.7	10.35
Total 2006-2010	13(100)	17 (100)	1223(100)		

DISCUSSION

Rubella is a contagious respiratory disease which spreads throughout the world sporadically (1). According to the results of this study in the last few years an increasing trend of the rubella incidence was noted in Republika Srpska. The largest number of cases involves teenagers (12,13). Similar results were presented in a study by Boxal et al, which has noted the absence of revaccination and vaccination with only monovalent vaccine against measles as one of the main reasons of increased number of rubella infection.(7)

The results of this study have shown that generations born between 1990 and 1994 were most affected, when regular immunization with MMR vaccine was not carried out and only monovalent measles vaccine was used instead. According to some authors an increasing number of rubella cases occured in areas where no regular immunization was applied, and where control of immunization was not carried out regularly, e.g. in rural areas and in multi-ethnic communities where there are different cultural understandings and lower level of education of the population (8).

The results of this study have shown that the majority of patients were from the southeast part of Republika Srpska. All epidemics in these areas were suppressed spontaneously or by implementing measures with MMR immunization.

In the postwar period, until 1998, mandatory vaccination was not carried out in some parts of Republika Srpska due to unavailability of vaccine. The situation was additionaly complicated because of the great migration of the population during the war when refugees from neighboring Republics came unvaccinated or with no previous evidence of the accomplished immunization (12,13). Also, after the war, coverage of immunization did not reach the desired level of 95%, therefore, generations of unvaccinated or incomplete vaccinated persons appeared (12,13).

Table 2. Incidence rate in the municipalities of Republika Srpska in the period 2006 - 2010

Municipality	Incidence rate (per 100 000 inhabitants)				
	Year				
	2006	2007	2008	2009	2010
Banja Luka	0.2	0.14	0.14	31.0	1.5
Bijeljina	0.7	0	0.6	2.1	15.3
Doboj	0.7	0	0	3.3	11.4
Zvornik	0	0	0	0	34.9
Istočno Sarajevo	0	0	0	185.4	337.5
Foča	0	0	0	1.5	45.6
Trebinje	2.5	0.25	1.23	70.4	367.9

During our investigation it was noted that the first major increase of the disease was in 2009.

Ang et al. have shown that the decreasing number of cases was associated with the percentage of success in the immunization in the most vulnerable population groups such as soldiers and recruits in the army, pregnant women and children, immigrants, and students from foreign countries or other cities (9).

In most studies special attention was paid to the prevention of congenital rubella syndrome, which is the consequence of rubella infection during pregnancy, especially during the first sixteen weeks, which could result in miscarriage, fetal death, or infants born with birth defects (10).

As of 17 May 2010 the Institute of Public Health in Banja Luka and the Ministry of Health and Social Welfare of Republika Srpska, in addition to other counter-epidemical measures, have intensified active epidemiological surveillance especially for pregnant women and school children. The mandatory control of pregnant women was introduced, particularly for those from affected areas. In relation to our results it could be expected that the number of rubella cases would be lower thus far (11).

Inadequate immunization, migration and lack of funds caused a reduction in the overall level of public health and health system which led to a drastic increase in number of rubella cases in Republika Srpska. The increase in the number of infected persons represents a hazard for potential complications of rubella, which should accelerate the introduction of comprehensive immunization and its control in the population, especially in areas with less resources and in areas where public health awareness is low.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Centers for Disease Control and Prevention-CDC. Achievements in public health: elimination of rubella and congenital rubella syndrome-United States, 1969-2004. MMWR 2005, 54:279-82.
2. Plotkin SA, Reef SE. Rubella vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 5th ed. Philadelphia: Saunders, 2008:735–71.
3. Cutts FT, Vynnycky E. Modelling the incidence of congenital rubella syndrome in developing countries. Int J Epidemiol 1999; 28:1176 – 84.
4. Reef SE, Strebel P, Dabbagh A, Gacic-Dobo M, and Cochi S. Progress toward control of rubella and prevention of congenital rubella syndrome-worldwide, 2009. J Infect Dis 2011; 204 (suppl 1):24-7.
5. World Health Organization. World Health Statistics 2010th www.who.int/whosis/whostat/2010/en/index.html
6. Republic Institute for public health "Dr Milan Jovanovic Batut". Health Statistics Yearbook of the Republic of Serbia, Infectious Diseases. Beograd: Republic Institute for public health "Dr Milan Jovanovic Batut", 2009:229-48.
7. Boxall N, Kubinyiova M, Príkazský V, Benes C, Cástková J. An increase in the number of mumps cases in the Czech Republic, 2005-2006. Euro Surveil 2008; 13:1-4.
8. Metcalf CJ, Bjornstad ON, Ferrari MJ, Klepac, P, Bharti N, Lopez-Gatell H, Grenfell BT. The epidemiology of rubella in Mexico: seasonality, stochasticity and regional variation. Epidemiol Infect 2010; 15:1-10.
9. Ang LW, Chua LT, James L, Goh KT. Epidemiological surveillance and control of rubella in Singapore, 1991-2007. Ann Acad Med Singapore 2010; 39:95-101.
10. Robertson SE, Cutts FT, Samuel R, Diaz-Ortega JL. Control of rubella and congenital rubella syndrome (CRS) in developing countries. Part 2: vaccination against rubella. Bull World Health Organ 1997; 75:69-80.
11. Republika of Srpska Government. Službeni glasnik of the Republika Srpska. 2008, No 41.
12. Novo A, Huebschen JM, Muller CP, Tesanovic M, Bojanic J. Ongoing rubella outbreak in Bosnia and Herzegovina, march-july 2009-preliminary report. Euro Surveill 2009; 14:1-4.
13. Institut za zaštitu zdravlja Republike Srpske. Zarazne i parazitarne bolesti na teritoriji Republike Srpske. Banja Luka: Institut za zaštitu zdravlja Republike Srpske, 2010: 22.

Porast incidencije rubele u Republici Srpskoj u periodu od 2006. do 2010. godine

Veljko Ćejić[1], Tamara Naumović[2]

[1]Gradski zavod za javno zdravlje, [2]Institut za medicinsku statistiku i informatiku, Medicinski fakultet, Univerzitet u Beogradu; Beograd, Srbija

SAŽETAK

Cilj ove studije bio je istraživanje stope incidence rubele u Republici Srpskoj, u periodu od 2006. do 2010. godine. Ukupno 1.236 slučajeva rubele prijavljeno je u toku izveštajnog perioda, s višestrukim povećanjem stopa incidencije, od 0,5 u 2006. na 54,7 na 100.000 stanovnika u 2010. godini. U poslednje dve godine posmatranog perioda, u Republici Srpskoj je došlo do pojave epidemija. Neadekvatna imunizacija, migracija stanovništva i nedostatak sredstava, uslovili su smanjenje ukupnog nivoa javnog zdravlja i zdravstvenog sistema, što je dovelo do drastičnog povećanja broja slučajeva obolelih od rubele.

Ključne reči: rubela, incidencija, imunizacija

CASE REPORT

Six years of following up a glomus jugulare tumor - a case report

Ivanka Štenc Bradvica[1], Davor Jančuljak[1], Silva Butković-Soldo[1], Ivan Hećimović[2]

[1]Department of Neurology, [2]Department of Neurosurgery; University Clinical Center of Osijek, Osijek, Croatia

Corresponding author:

Ivanka Štenc Bradvica; Department of Neurology, University Clinical Center in Osijek; J. Huttlera 4, 31 000 Osijek, Croatia

Phone: +385 31 512 361; fax.: +385 31 512 216

E-mail: stenc-bradvica.ivanka@kbo.hr

Original submission: 21 February 2011; **Revised submission**: 14 July 2011; **Accepted**: 14 July 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):112-114

ABSTRACT

This case report followed up a patient for six years after she had been successfully treated by embolization and gamma knife surgery, while a complete surgical resection was contraindicated because of the high risk of possible mortality outcome. A development of internal hydrocephalus in a subacute postoperative period as a probable postoperative complication related to gamma knife surgery was noted.

Key words: glomus jugulare, tumor, embolization, gamma knife surgery

INTRODUCTION

Glomus jugulare tumors are rare, slow-growing, hypervascular tumors that arise within the jugular foramen of the temporal bone (1). These tumors often go unnoticed, because of the insidious onset of symptoms and delay in diagnosis is frequent (2). Due to the location and extent of involvement, glomus jugulare tumors present a significant diagnostic and treatment challenge (3). The most common symptoms of glomus jugulare tumors are tinnitus, aural pulsations, decreased hearing, ear pain and vertigo (4). In some cases tumors can cause lesions of the VII, VIII, IX, X and XI cranial nerves (5).

The standard surgical treatment is often connected with high mortality and morbidity due to its high vascularisation and location, so less invasive and palliative treatments are optionally performed (6). Therefore less invasive treatment like preoperative embolization, radiation therapy and stereotactic radiosurgery or their combination are used (7). In patients with residual peripheral facioparesis due to delayed and incomplete recovery of the nerve an ocular surgical treatment by implanting gold weight eyelid into the musculus levator palpaebre is needed (8). A very rare complication of developing an internal hydrocephalus has been reported, as a complication due to surgery (9).

The aim of this case report was to outline the variability of clinical presentation which is leading to the implementation of demanding diagnostic methods.

CASE REPORT

A 68-year old female patient was treated for dysphonia by an otorynolaryngologist during 2004. One year later she was referred to a neurologist because of developing left peripheral facioparesis, hypotrophy of left shoulder muscles, left hemi hypotrophy of tongue and left ear hearing loss. Diagnostic work-up included tonal audiogram, conventional CT scans of brain and 3D CT reconstruction of temporal bone, MR brain scan, 3D CT angiography and digital substracted angiography (Figure 1), electromyoneurography and auditory evoked brain potentials.

We diagnosed a hypervascular tumor by the left pyramid eroding the bone tissue and invading the middle ear and the external auditory canal. Left internal carotid artery was incorporated into the tumor, and the jugular vein bulb was pushed dorsally by the glomus. The glomus was well fed by the ramifications of the left external carotid artery

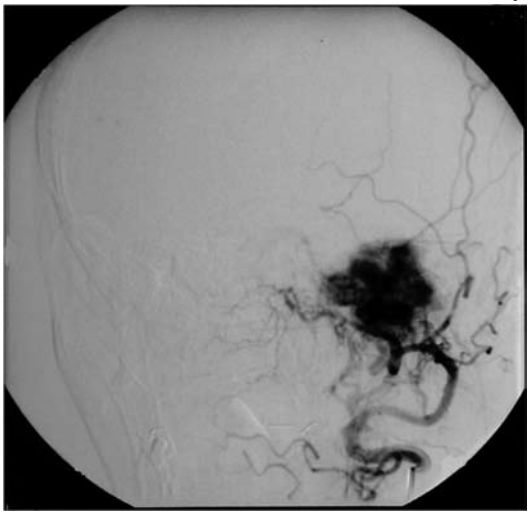


Figure 1. Digital subtracted angiography showing a highly vascular tumor (Štenc Bradvica I, 2005)

and by the left internal carotid artery. The treatment was started with embolization of two from three feeding vessels, and the tumor size was reduced by 40%. We assessed that in our patient the standard surgery was contraindicated so gamma-knife surgery was applied.

About six to seven months after the treatment, the patient complained about frequent headaches, dysphagia, gradual urine incontinence, complained about gait disability and mild cognitive deterioration. Brain magnetic resonance did not show any further tumor expansion. The development of internal hydrocephalus was suspected so she was treated by the neurosurgeon and the ventriculo-peritoneal drainage was performed. Shortly after that procedure had been performed, we registered a good recovery of gait and cognition in our patient.

The patient is feeling well, she is regularly controlled by a neurologist and neurosurgery specialist and the follow-up showed no further growth of the tumor and no deterioration of neurological deficit (Figure 2).

Some authors reported selective embolization as an effective technique which can bring to shrinking of the tumor size and significantly decrease blood loss during a later surgical treatment (10, 11). Beside embolization and resection, the radiation therapy is equally efficient. In some cases gamma knife therapy is the only option of treatment due to the extension of tumor and the risk effects of possible surgery (12, 13).

Postoperative complications of the conventional glomus tumor surgery may include a development of internal hydrocephalus in subacute postoperative period (13). In our patient we observed a more insidious development of hydrocephalus after the gamma knife surgery. We think that it was not related to the tumor expansion, but more likely it occurred as a late neurological complication of gamma knife surgery.

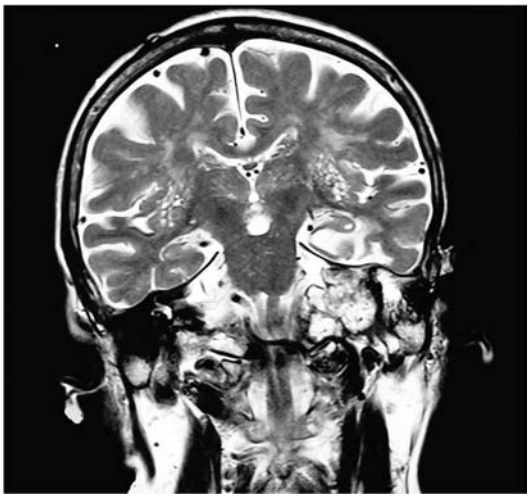


Figure 2. Brain magnetic resonance showing glomus jugulare tumor on the left side without further progression during the period of six years (Štenc Bradvica I, 2011)

As in patients with residual peripheral facioparesis due to delayed and incomplete recovery of the nerve, an ocular surgical treatment is needed, which was successfully performed in our patient (14).

Full clinical presentation of the glomus jugulare tumor in our patient occurred in the advanced stage of the disease. A complex combination of diagnostic methods was necessary performed for evaluating the diagnosis. The combination of less invasive treatment of preoperative embolization and gamma knife surgery was used, sparing the patient from additional tissue damage and operative complications.

Internal hydrocephalus as a rare post-radiosurgery complication, which developed in our patient, was treated well by implanting a ventriculo-peritoneal drainage.

In conclusion, after a period of six years from embolization and gamma knife surgery our patient is feeling well, without any new neurological signs which would indicate the progression of the tumor size. The neuroimaging diagnostic methods like brain magnetic resonance did not show any further tumor expansions.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Ramina R, Maniglia JJ, Fernandes YB, Paschoal JR, Pfeisticker LN, Coelho Neto M. Tumors of the jugular foramen: diagnosis and managment. Neurosurgery 2005; 57:59-68.
2. Zemba M, Cucu B, David L, Stinghe A, Furedi G, Halmaci V, Enache V, Lacusteanu M. Glomus tumor with diplopia. Oftalmologia 2009; 53: 85-9.
3. Al- Mefty O, Texeira A. Complex tumors of the glomus jugulare: criteria, treatment, and outcome. J Neurosurg 2002; 97:1356-66.
4. Guss ZD, Batra S, Li G, Chang SD, Parsa AT, Rigamonti D, Kleinberg L, Lim M. Radiosurgery for glomus jugulare: history and recent progress. Neurosurg Focus 2009; 27:1-6.

5. Ivan ME, Sughrue ME, Clark AJ, Kane AJ, Aranda D, Barani IJ, Parsa AT. A meta- analysis of tumor control rates and treatment-related morbidity for patients with glomus jugulare tumors. J Neurosurg 2011; 114:1299-305.
6. Morgan MS, Fahmy OM. The safety and efficacy of gamma knife surgery in managment of glomus jugulare tumor. World J Surg Oncol 2010; 8:76.
7. Chen PG, Nguyen JH, Payne SC, Sheehan JP, Hashisaki GT. Treatment of glomus jugulare tumors with gamma knife radiosurgery. Laryngoscope 2010; 120:1856-62.
8. Rofagha S, Seiff SR. Long-term results for the use of gold eyelid load weights in the management of facial paralysis. Plast Reconstr Surg 2010; 125:142-9.
9. Perez-Mora R, Lassaletta L, Gavilan J. Intracranial hypertension: a rare complication following glomus jugulare surgery. Int Adv Otol 2009; 5:277-80.
10. Young NM, Wiet RJ, Russell EJ, Monsell EM. Superselective embolization of glomus jugulare tumors. Ann Otol Rhinol Laryngol 1988; 97:613-20.
11. Girolami G, Heuser L, Hildmann H, Sudhoff H. Selective embolization and surgical resection for head and neck glomus tumours-clinical outcome analysis. Laryngorhinootologie 2008; 87:181-5.
12. Sheehan J, Kondziolka D, Flickinger J, Lunsford L D. Gamma knife surgery for glomus jugulare tumors: an intermediate report on efficacy and safety. J Neurosurg 2005; 102:241-6.
13. Navarro MA, Maitz A, Grills IS, Bojrab D, Kartush J, Chen PY, Hahn J, Pieper D. Successful treatment of glomus jugulare tumours with gamma knife radiosurgery: clinical and physical aspects of managment and review of the literature. Clin Transl Oncol 2010; 12:55-62.
14. Schrom T, Buchal A, Ganswindt S, Knippping S. Patient satisfaction after eyelid loading in facial palsy. Eur Arch Otorhinolaryngol 2009; 266:1727-31.

Šestogodišnje praćenje glomus jugulare tumora - prikaz slučaja

Ivanka Štenc Bradvica[1], Davor Jančuljak[1], Silva Butković-Soldo[1], Ivan Hećimović[2]

[1]Klinika za neurologiju, [2]Klinika za neurokirurgiju; Klinički bolnički centar Osijek, Osijek, Hrvatska

SAŽETAK

U ovom radu je prikazan slučaj bolesnice nakon uspješnog tretmana glomus jugulare tumora pomoću embolizacije i kirurgije gama nožem, tijekom šest godina nakon zahvata. Potpuna kirurška resekcija tumora kod ove bolesnice bila je kontraindicirana zbog visokog rizika od smrtnog ishoda. Razvoj internog hidrocefalusa, do kojeg je došlo u subakutnom periodu, postoperativna je komplikacija kirurškog zahvata gama nožem.

Ključne riječi: glomus jugulare tumor, embolizacija, kirurgija gama nožem

CASE REPORT

Atrial myxoma as a cause of stroke: emboli detection and thrombolytic treatment

Svetlana Ružička-Kaloci, Petar Slankamenac, Branka Vitić, Aleksandra Lučić-Prokin, Mirjana Jovićević, Željko Živanovic, Dragica Hajder.

Clinic of Neurology, Clinical Centre of Vojvodina, Novi Sad, Serbia

Corresponding author: Svetlana Ružička-Kaloci; Clinic of Neurology, Clinical Centre of Vojvodina, Novi Sad, Serbia; Hajduk Veljkova 1, 21000 Novi Sad, Serbia;

Phone: +381 21 484 3632; fax.: +381 21 526 520 ;

Email: ruzickakaloci@gmail.com

Original submission: 29 April 2011; **Revised submission**: 20 September 2011; **Accepted**: 29 September 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):114-117

ABSTRACT

It presents a case of a 42-year-old female patient who was admitted to the stroke unit for right-sided hemiplegia and global aphasia, without conventional stroke risk factors. As the patient presented within the therapeutic time window and had no contraindications for thrombolysis, intravenous thrombolytic treatment was initiated. Brain CT showed multiple hypodense partly confluent lesions in the territory of the left middle cerebral artery. For the purpose of determining the etiology of the stroke, TCD was performed and after cerebral microemboli were detected, transthoracic echocardiography was indicated, the finding of which showed the presence of a myxoma in the left atrium. The patient underwent surgery and thereafter her neurological deficits improved.

Key words: myxoma, ischemic stroke, transcranial doppler, cerebral microemboli, intravenous thrombolysis

INTRODUCTION

Cardiac myxoma is a benign primary tumor of the heart that occurs twice as often in women as in men, in 75% of cases in the left atrium (1). In 90% of patients it is diagnosed at the age 30-60 years (2). Atrial myxoma is a sporadic type of tumor, however, in 7% of cases it has familial occurrence (3). It might be accompanied by aneurysmal dilatations of intracranial blood vessels, and in that case it might result in intracerebral or subarachnoid hemorrhage (3).

Clinically, myxoma manifests in signs of systemic embolism, intracardiac obstruction it might be a cause of cardiogenic shock or sudden cardiac death) or in the presence of general nonspecific symptoms that frequently go unrecognized, such as myalgia, arthralgia, increased body temperature, etc. (4).

Emboli originating from atrial myxoma consist of thrombotic mass, tumor tissue, or a combination of the two. Embolism occurs in 20-45% of cases, often as the first clinical manifestation (4). In the majority of cases, cerebral arteries are involved and the disease manifests itself in neurological symptoms, such as ischemic stroke, syncope, headache, and seizure. The stroke is often recurrent with a clinical picture of progressive multi-infarct dementia or fatal embolic stroke (5).

CASE REPORT

A 42-year-old female patient, mother of four children, was admitted to the stroke unit for right-sided hemiplegia and global aphasia, without conventional stroke risk factors and with a long history of headache. Her National Institute of Health Stroke Scale (NIHSS) score was 17. As the patient was presented within the therapeutic time window and without contraindications for thrombolysis, intravenous thrombolytic treatment was initiated.

An initial brain CT scan was normal (ASPECT score 10) and the patient was administered an appropriate dose of recombinant tissue plasminogen activator (rtPA). A subsequent brain CT scan made after 24 hours showed multiple hypodense partly confluent lesions in the territory of the left middle cerebral artery (MCA). For etiological purposes, Duplex ultrasonography of the neck blood vessels was performed, and the finding was within the normal range. A bubble test was performed and was negative. During 40-minute TCD monitoring, cerebral microembolic signals were detected over both MCAs (Figure 1).

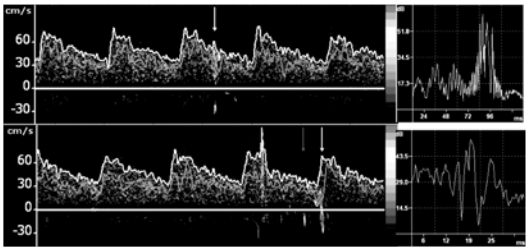


Figure 1. Characteristic microembolic signals detected over the MCA at the depth of 53mm during an acute phase of ischemic stroke in our patient (Ružička-Kaloci S., 2011)

Since solid microembolic signals were detected over the MCA bilaterally, a cardiac source of the emboli was suspected, and contrast transesophageal or transthoracic echocardiography was indicated. The ECG finding was normal, as well as auscultation over the heart. On echocardiography, echo formation (size 4.5x2cm) was registered in the left atrium, of uneven echogenicity and irregular surface, with high embolic potential, corresponding to a myxoma originating from the proximal part of the interatrial septum. During diastole it protruded through the mitral opening in the left ventricle (Figure 2).

Routine laboratory analysis detected an increased sedimentation rate. Subsequent anamnesis did not show the existence of other nonspecific symptoms or cardiological complaints. During the hospitalization, the neurological deficit significantly improved (NIHSS score 8, modified Rankin score 4).

As indicated by consultant cardiologist, the patient was urgently transferred to the Institute for

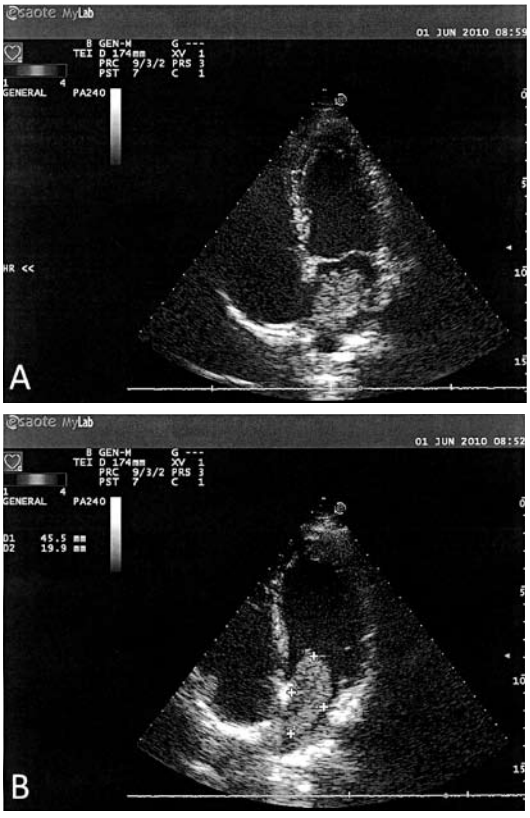


Figure 2. Preoperative transesophageal echocardiography. A) Myxoma of the left atrium, B)the myxoma protruding through the mitral opening in the left ventricle during diastole (Ružička-Kaloci S., 2011)

Cardiovascular Diseases, where the myxoma was resected. On a follow-up neurological examination, the neurological deficit was further improved (NIIHSS score 4), and no microemboli were seen on a repeated TCD examination.

Cardiac myxomas represent a rare cause of ischemic stroke (6, 7). Since the majority of myxomas are localized in the left atrium, signs of systemic embolism are common (8). Patients presenting with neurological complications of cardiac myxomas are usually young, and stroke is frequently the first clinical manifestation, as illustrated by our case report (6).

Transthoracic echocardiography (TTE), computed tomography (CT) and magnetic resonance imaging (MRI) can accurately determine the size, localization and mobility of the tumor (1). Preoperative transthoracic echocardiography is an initial diagnostic method and often the method of choice that is able to define the type, location and structure of the tumor mass, whereas surgical resection is an emergency procedure and a definitive method of primary and secondary stroke prevention (8).

Detection of cerebral microemboli by TCD is one of the ultrasonographic noninvasive diagnostic procedures that may be useful in showing the mechanism of the development of stroke (in the case cerebral microemboli are detected), as well as the source of cerebral embolism, which can determine further diagnostic procedures aimed at establishing the precise etiology (9). In our case, the presence of cerebral microemboli suggested high embolic potential of the myxoma, which prompted cardiac surgeons to perform emergency surgery. Literature data on TCD monitoring in patients with cardiac myxoma are scarce, and in a single report we found, the authors did not detect microemboli in their patient with acute cardioembolic stroke due to atrial myxoma (10).

In order to speedily determine the etiology of ischemic stroke in young people without risk factors for CVD, it is necessary to exhaust all available noninvasive diagnostic methods.

On the other hand, data on the application of intraarterial and intravenous thrombolysis for acute cerebral ischemia in patients with atrial myxoma are more numerous. However, the role of thrombolysis in the treatment of these patients is still unclear (11). The benefit of thrombolysis could be expected in the case of occlusion of blood vessels by emboli made of thrombotic mass, whereas in the case of embolism by tumor tissue itself, thrombolysis would probably have no beneficial effect (12). Despite the danger of possible complications, such as intracerebral hemorrhage, the application of thrombolytic treatment may be beneficial in the treatment of patients with atrial myxoma (11), as our case report corroborates.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Velicki L, Nicin S, Mihajlovic B, Kovacevic P, Susak S, Fabri M. Cardiac myxoma: clinical presentation, surgical treatment and outcome. J BUON 2010; 15:51-5.
2. Sarjeant JM, Butany J, Cusimano RJ. Cancer of the heart; epidemiology and management of primary tumors and metastases. Am J Cardiovasc Drugs 2003; 3:407-21.
3. Al-shahi Salman R, Northridge D, Graham AN, Grant R. Stroke due to a cardiac myxoma. Pract Neurol 2007; 7:52-5.
4. O'Rurke F, Dean N, Mouradian MS, Akhtar N, Shuaib A. Atrial myxoma as a cause of stroke: case report and discussion. CMAJ 2003; 169:1049-51.
5. Bienfait HP, Moll LC. Fatal cerebral embolism in young patient with an occult left atrial myxoma. Clin Neurol Neurosurg 2001; 103:37-8.
6. Ekinci EI, Donnan GA. Neurological manifestations of cardiac myxoma: a review of the literature and report of cases. Intern Med J 2004; 34:243-9.
7. Jovićević M, Divjak I, Slankamenac P, Božić K, Rabi-Žikić T, Ružička Kaloci S. Najčešći uzroci ishemičnog moždanog udara kod mladih osoba. Med Pregl 2011; 64:331-5.
8. Ugurlu B, Oto O, Okutan H, Kutluk K, Silistrel E, Sariosmanolu N, Hazan E, Kargi A. Stroke and myxoma. Asian Cardiovasc Thorac Ann 2000; 8:130-3.
9. Marcus H. Monitoring Embolism in Real Time. Circulation 2000; 102-826.
10. Telman G, Mesica O, Kouperberg E, Cohen O, Bolotin G, Agmon Y. Microemboli monitoring by transcranial doppler in patient with acute cardioembolic stroke due to atrial myxoma. Neurology international 2010; 2:24-7.
11. Nagy CD, Levy M, Mulhearn TJ, Shapland M, Sun H, Yuh DD, Cheung D, Chandra-Strobos N. Safe and effective intravenous thrombolysis for acute ischemic stroke caused by left atrial myxoma. J Stroke Cerebrovasc Dis 2009; 18:398-402.
12. Ibrahim M, Iliescu C, Safi HJ, Buja ML, McPherson DD, Fuentes F. Biatrial myxoma and cerebral ischemia successfully treated with intravenous thrombolytic therapy and surgical resection. Tex Heart Inst J 2008; 35:193-5.

Atrijalni miksom kao uzrok ishemičnog moždanog udara: detekcija embolusa i trombolitički tretman

Svetlana Ružička-Kaloci, Petar Slankamenac, Branka Vitić, Aleksandra Lučić-Prokin, Mirjana Jovićević, Željko Živanovic, Dragica Hajder

Klinika za neurologiju, Klinički centar Vojvodine

SAŽETAK

U radu je prikazan slučaj četrdesetdvogodišnje pacijentkinje, primljene u jedinicu za moždani udar zbog desnostrane hemiplegije i globalne afazije, a bez konvencionalnih faktora rizika za moždani udar (MU). Obzirom da je pacijentkinja došla u predviđenom vremenskom intervalu i da je bila bez propratnih kontraindikacija, započet je terapijski postupak intravenske trombolize. Kontrolni CT mozga pokazivao je mrljaste hipodenzne, delom slivene promene u slivu leve arterije cerebri medije. U cilju utvrđivanja etiologije MU načinjena je i detekcija cerebralnih mikroembolusa (ME) transkranijalnim Dopplerom, a nakon detektovanih ME indikovana je transtorakalna ehokardiografija, te je nalaz ukazivao na prisustvo miksoma u predelu leve pretkomore. Bolesnica je operisana, pa je u daljem toku došlo do značajne regresije neurološkog deficita.

Ključne reči: miksom, ishemični moždani udar, transkranijalni Doppler, cerebralni mikroembolusi, intravenska tromboliza

CASE REPORT

Three-dimensional transvaginal ultrasonographic view of intact cornual pregnancy

Aleksandar Dobrosavljević[1], Svetlana Janković Ražnatović[2], Branko Dobrosavljević[1]

[1]Private Gynecological Practice "Demetra", Loznica, [2]Narodni Front Clinic of Gynecology and Obstetrics, Belgrade; Serbia

Corresponding author: Aleksandar Dobrosavljević; Private Gynecological Practice "Demetra"; Hajduk Stanka 9A, 15300 Loznica, Serbia; Phone: +381 1 587 70 47; fax: +381 1 589 71 60; E-mail: apotekaachillea@yahoo.com

Original submission: 01 April 2011; **Revised submission**: 13 May 2011; **Accepted**: 31 May 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):117-120

ABSTRACT

This work presents the case of the cornual ectopic pregnancy of a twenty year old patient who came to be examined due to a**menorrhea which had lasted for seven weeks**. Two-dimensional transvaginal ultrasound uncovered the existence of an intact ectopic pregnancy. Use of three-dimensional transvaginal ultrasound in a coronal section confirmed the diagnosis of cornual ectopic pregnancy, and the patient underwent laparatomy. Given that three-dimensional ultrasound enables excellent anatomical orientation and precise localization of pathological findings, especially in the coronal plane of the uterus, it can be expected that this technological advance can improve accuracy in diagnosis of cornual ectopic pregnancy.

Key words: cornual pregnancy, ectopic pregnancy, three-dimensional transvaginal ultrasound, two-dimensional transvaginal ultrasound.

INTRODUCTION

Ectopic pregnancy involves the implantation of a blastocyst outside of the uterine cavity.

In more than 95% of cases the place of implantation is the Fallopian tube, most frequently its ampullar section (in about 79% of all tubular pregnancies) (1). A cornual pregnancy involves implantation in the cornual or in the interstitial section of the tube (2). Cornual pregnancy is among very infrequent pregnancies, representing about 2% of all forms of ectopic pregnancy (3), after abdominal, ovarian and cervical ones (4). Seeing that the interstitial or cornual pregnancy is situated in a well vascularized muscular part of the tube or cornu uteri, such histological structure of these anatomical parts enables the pregnancy to be maintained longer than in other ectopic localities (4). In addition to this, the rupture of such a well vascularized structure provides a more dramatic clinical picture than in other forms of ectopic pregnancy. which are usually accompanied by shock and extensive intra-abdominal bleeding (2). The mortality percentage is twice as high as in other forms of ectopic pregnancy (5). Although some authors have introduced criteria based on 2D ultrasound for the definitive diagnosis of cornual pregnancy, misdiagnosis is still common (6). Transvaginal 3D ultrasound with its capacity to reproduce the coronal plane of the uterus, facilitates exact localization of the gestational sac relative to the uterine cornu (7).

This paper describes a case of a cornual pregnancy that was diagnosed by using two-dimensional (2D-TVUS) and confirmed by the three-dimensi-

onal transvaginal ultrasound (3D-TVUS) in the seventh week of gestation. We have attempted to indicate the significance of 3D-TVUS, particularly coronal plane of the uterus, which in that way enables the determination of accurate position of gestational sac as well as its relation to both uterine cornu and cavity.

CASE REPORT

A twenty year old women with no previous labors or miscarriages reported for an examination due to a**menorrhea** lasting for seven weeks, accompanied by bleeding. The patient did not complain of any pain. The patient's menstrual cycle had not been regular before the pregnancy. She had had no earlier surgical intervention and neither had she suffered from any other illnesses.

On admission, her vital parameters were normal and the patient was stable. A bimanual gynecological examination showed the uterus to be somewhat larger and softer and the right adnexa were thicker and slightly painful to palpation. The examination with the speculum revealed a small degree of bleeding ex utero. Examination by 2D TVUS showed empty uterus and decidual changes in the endometrium with a thickness of 13.82 mm. Image of the right adnexa showed the gestational sac which was measured 1.27 cm x 1.24 cm. The echo from the embryo was also noticeable as well as heart activity but it was not clearly visible in which part of the fallopian tube the gestational sac was situated. The ultrasound did not present any fluid in the Douglas pouch. The field of improved vascularization was mapped with the Color Doppler ultrasonography in the area near gestational sac. Examination by 3D-TVUS confirmed the diagnosis and also enabled better visualization of the anatomy of the uterus in its coronal plane. Namely, coronal plane determined more precisely the position of the gestational sac in relation to the uterine cavity (Figure 1), something that was hindered by the 3D-transvaginal transversal sectional plane (Figure 2). The B-hCG level was 5634 mIU/ml.

Twenty four hours after admission, the patient underwent laparotomy. An extirpation of the ovular tissue was carried out followed by suturing of the right uterine cornu. A histopathological analysis of the material confirmed the presence of chorionic villi. The post operative period went normally and the patient was discharged in good general condition. At this moment, the patient is in the 20th week of gestation, which is normal.

DISCUSSION

Reasons for the emergence of an interstitial or cornual pregnancy are not completely clear (8). The history of previous ectopic pregnancies terminated with ipsilateral salpingectomia is a common process with such patients (8). Modern assisted reproductive technology (ART) plays a very important role in increasing the incidence of the emergence of all forms of ectopic pregnancy and from there to the emergence of cornual pregnancy (9). In many cases, there is no clearly visible cause (5). Because of the specific locality, an early diagnosis of cornual pregnancy is often impeded (5). The use of the 2D-TVUS associated with the Color Doppler has increased the diagnostic sensibility of tubal gestation; however, it is still difficult to define the location of the gestational sac and its relation to the uterus and the attachments. (5).

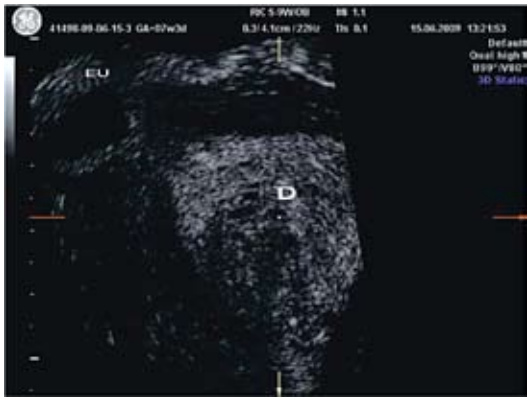


Figure 1. Transvaginal three-dimensional coronal sectional plane of the uterus (Eu, cornual ectopic pregnancy with eho of the embrion in the right cornu of the uterus; D, deciduas) (Dobrosavljevic A., 2009)

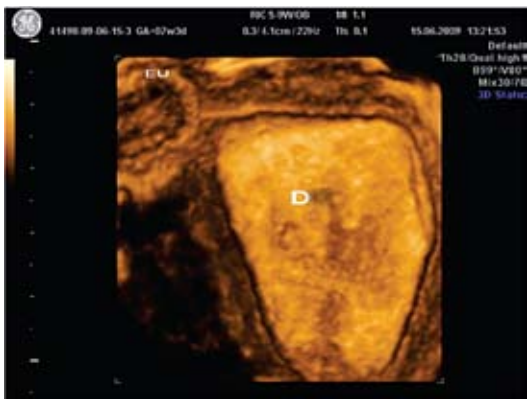


Figure 2. Transvaginal three-dimensional rendering technique (Eu, cornual ectopic pregnancy; D, deciduas) (Dobrosavljevic A., 2009)

Characteristic signs of cornual pregnancy are the absence of a gestational sac in the uterine cavity, an eccentrically or completely laterally located gestational sac and the presence of a myometrium between the gestational sac and the uterine cavity (4, 10). The pulsed Doppler signals of an ectopic pregnancy are typically of low impedance and high diastolic flow, although a significant range of Doppler waveforms may be observed (10). In addition, color flow may also vary widely. It can show vascular ring, which indicates an intense peri-trophoblastic vascular activity or bizarre pattern of color flow. (5,10). The 3D-TVUS with its capacity to reproduce the coronal plane of the uterus, facilitates exact localization of the gestational sac relative to the uterine cornu. (7). An additional advantage is the possibility of the retrograde processing of previously memorized information (volume), as well as the possibility of removing any artifacts caused by neighboring anatomic structures (11). The choice of the method of treating ectopic pregnancy depends on a number of factors, such as localization, the size of the gestational sac or an invasion of the surrounding structure, whether the patient has already given birth or is planning a pregnancy, and also whether it is going to develop into the rupture of an extra uterine pregnancy (1). Taking everything into account, either laparoscopic or classical surgical treatment can be planned (12). The use of methotrexate controlled by ultrasound has also proved to be a method that has given good results (7,13). The selective embolization of the uterine artery has also been described as a method which reduces blood loss (7, 13).

In the following surgical treatment, the size of the gestational sac, maintaining the fertility of the patient as well as the experience of the surgeon are also factors of extreme importance when making a decision on the type of treatment to be administered to this form of ectopic pregnancy (1). Laparotomy remains the chosen treatment in case of ruptured cornual pregnancy (12). However, in case of an intact form of cornual pregnancy, the remaining forms of therapy can be considered (4, 14). At the moment there is not sufficient evidence to give priority to any particular form of therapy (13).

2D-TVUS still remains the primary method in diagnostics of ectopic pregnancy. But in case when determining precise localization of gestational sac is of great importance as in case of cornual ectopic pregnancy, 3D-TVUS, as a relatively new technology, which provides additional certaainty in making diagnosis. A more reliable diagnosis allows us to plan adequate treatment and reduction of morbidity.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Rajab KE, Issa A, Sandhu AK. Interstitial pregnancy. BMB 2006; 28:95-97.
2. Timor-Tritsch IE, Monteagudo A, Lerner JP. A ''potentially safer'' route for puncture and injection of cornual ectopic pregnancies. Ultrasound Obstet Gynecol 1996; 7: 353–5.
3. Izquierdo LA, Nicholas MC. Three-dimensional transvaginal sonography of interstitial pregnancy. JCU 2003; 31: 484–7.
4. Fritz MA, Speroff L. Clinical gynecologic endocrinology and infertility. 8th ed. Philadelphia, PA: 2011: 1410.
5. Araujo EJ, Filho SMZ, Pires CR, Filho HAG, Massaguer AA, Nardozza LMM, Moron AF. Three-dimensional transvaginal sonographic diagnosis of early and asymptomatic interstitial pregnancy. Arch Gynecol Obstet 2007; 275:207-10.
6. Jermy K, Thomas J, Doo A, Bourne T. The conservative management of interstitial pregnancy. BJOG 2004; 111:1283–8.
7. Valsky DV, Hamani Y, Verstandig A, Yagel S. The use of 3D rendering, VCI-C, 3D power Doppler and B-flow in the evaluation of interstitial pregnancy with arteriovenous malformation treated by selective uterine artery embolization. Ultrasound Obstet Gynecol 2007; 29:352-5.
8. Advincula AP, Senapati S. Interstitial pregnancy. Fertil Steril 2004; 82:1660-1.
9. Revel A, Ophir I, Koler M, Achache H, Prus D. Changing etiology of tubal pregnancy following IVF. Hum Reprod 2008; 23:1372–6.
10. Emery A, Buentipo B. Sonographic detection of cornual ectopic pregnancy: case report. JDMS 2008; 24:252–6.
11. Anadakumar C, Mohammed NB. Three-dimensional transvaginal sonographic diagnosis of asymptomatic interstitial pregnancy at 6 weeks of gestation. Acta Obstet Gynecol Scand 2004; 83:408-10.
12. Moawad NS, Dayaratna S, Mahajan ST. Mini-cornual excision: a simple stepwise laparoscopic technique for the treatment of cornual pregnancy. JSLS 2009; 13:87–91.
13. Ophir E, Singer-Jordan J, Ottinger M, Odeh M, Tendler R, Feldman Y, Fait V, Bornstein J. Uterine artery

embolization for the management of two interstitial ectopic pregnancies: case report. Hum Reprod 2004; 19:1774-7.
14. Monteagudo A, Minior VK, Stephenson C, Monda S, Timor-Tritsch IE. Non-surgical management of live ectopic pregnancy with ultrasound-guided local injection: a case series. Ultrasound Obstet Gynecol 2005; 25: 282–8.

Trodimenzionalni ultrazvučni prikaz intaktne kornualne trudnoće

Aleksandar Dobrosavljević[1], Svetlana Janković Ražnatović[2], Branko Dobrosavljević[1]

[1]Specijalistička ginekološka ordinacija "Demetra", Loznica;
[2]Ginekološko akušerska klinika "Narodni front", Beograd; Srbija

SAŽETAK

U radu je prikazan slučaj kornualne ektopične trudnoće kod dvadesetogodišnje pacijentkinje koja se javila na pregled zbog amenoreje u trajanju od 7 nedelja. Dvodimenzionalnim ultrazvučnim pregledom dijagnostikovana je intaktna vanmaterična trudnoća. Pomoću trodimenzionalnog ultrazvuka, posebno koronalnog preseka uterusa, potvrđena je dijagnoza nakon čega je pacijentkinja operisana. S obzirom da trodimenzionalni ultrazvuk omogućava odličnu anatomsku orijentaciju, kao i preciznu lokalizaciju patološkog supstrata, posebno u koronalnom preseku uterusa, može se očekivati da ovaj tehnološki napredak poboljša sigurnost u postavljanju dijagnoze kornualne ektopične trudnoće.

Ključne reči: kornualna trudnoća, ektopična trudnoća, 3D transvaginalni ultrazvuk, 2D transvaginalni ultrazvuk.

CASE REPORT

Intermittent hepatic porphyria in pregnancy with good perinatal outcome

Domagoj Vidosavljević[1], Siniša Šijanović[2], Mirjana Rubin[2], Maja Košuta Petrović[2] Kristina Abičić Žuljević[2], Ivana Šimić[3]

[1]Department of Obstetrics and Gynaecology, Vukovar General Hospital, Vukovar; [2]Department of Obstetrics and Gynaecology, University Hospital Osijek, Osijek, [3] Community Health Care Center Đakovo, Đakovo, Croatia

Corresponding author: Domagoj Vidosavljevic, Department of Obstetrics and Gynaecology; Bolnička 5, 32000 Vukovar, Croatia; Phone: +385 32 336 054; fax.: +385 32 332 178; E-mail: d-vidosavljevic@inet.hr

Original submission: 27 March 2011; **Accepted**: 14 July 2011.
Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):120-122

ABSTRACT

Porphyrias are rare metabolic diseases caused by enzymatic defects of the haeme biosynthesis. Association of pregnancy and acute porphyria is rare, but mortality rate among pregnant women from acute attack has been reported up to 42%. This paper presents a patient with pregnancy complicated by intermittent hepatic porphyria with good perinatal outcome. The pattern of the attack in pregnancy varies individually and it makes porphyric pregnancies a challenge. Previously diagnosed porphyria patients should be closely monitored during pregnancy and diagnosis of acute porphyria must be also considered in all pregnant women with unexplained abdominal pain.

Key words: porphyria, pregnancy, perinatal outcome

INTRODUCTION

The porphyrias are a rare, heterogeneous group of primarily hereditary, metabolic diseases caused by a partial deficiency in one of the eight enzymes involved in the haem biosynthesis (1). Symptoms of the disease can present as acute attacks of abdominal pain and neuropsychiatric seizures (peripheral neuropathy, cortical symptoms, hallucinations, confusion, delusion, depression), skin symptoms, or both.

Acute attacks are triggered by various factors, such as endocrine changes, physical or emotional stress, alcohol consumption, smoking, and a wide array of drugs (2). Cutaneous symptoms consist of blistering and fragile skin on sun-exposed areas and photosensitization (3). Porphyrias are clinically classified into acute and cutaneous types based on their predominant symptoms, and into hepatic and erythropoetic types based on the major porphyrin production site. Acute types include acute intermittent porphyria, acute hepatic porphyria, variegate porphyria and hereditary coproporphyria (4). The association of pregnancy and acute porphyria is rare (5, 6). Although pregnancy may exacerbate or provoke an acute attack of porphyria, a first attack in pregnancy is very rare (7). The mortality rate from acute attack among pregnant women has been reported to be 42 % (8). That makes porphyria a challenging problem for obstetricians. Due to increased awareness of the disorder and proper management, the prognosis and both the maternal and foetal outcome was dramatically improved over the years (9).

CASE REPORT

A 36-year old primigravida was admitted to hospital at 37 weeks of gestational age. She had been tested and diagnosed for porphyria 10 years ago when she had presented with general weakness and cachexy and she was diagnosed with intermittent hepatic porphyria. Afterwards, she had recurrent attacks of weakness and acute abdominal pain. In 2004 she underwent partial embolisation of myoma (superselective embolisation of both uterine arteries) under local anaesthesia. During the pregnancy she was closely monitored keeping in mind factors and drugs known to precipitate attacks. In the 22nd week of gestation, due to imminent abortion she was prescribed with magnesium. Beside that course of pregnancy was uneventfull. In the 37th week of gestation she was admitted to our Department due to general feeling of weakness followed by hypotension (90/60 mm Hg). No contractions or abdominal pain was reported. Her blood parameters indicated anaemia (E 3,60x10^{12}/L, HGB 91 g/L, Htc 0,270, PLC 270x10^{9}/L), blood glucose level was 3,3 mmol/L. Urinary delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) were slightly increased, all other blood parameters were normal. The foetal heart tracings were normal. Cervix appeared a tip of a finger open. Ultrasound confirmed foetal breech presentation, with all other foetal parameters normal and appropriate for the gestational age. Next to isthmus a myoma measuring 6,4 x 8,2 cm was found. Taking into account all these aspects, a decision was made to perform the Caesarean section. Adequate hydration was done prior to the surgery in order to ensure normoglycaemia and electrolyte balance. Proprofol was used to induce general anaesthesia.

A healthy, male infant (3120/49) was delivered. Apgar score was 9/10. The postoperative course was uneventful. Methergin, diclofenac and metoclopramide were avoided in the postoperative course as a precaution. Pain was controlled with opiates and postpartum haemorrhage was avoided by intravenous infusion of syntocinon. There was also normosang (human hemin) ready to use in a case of attack. The patient was on a high-carbohydrate diet and maintained adequate fluid intake to ensure good clearance of porphyrins. Postoperative values of 24-hour urinary porphobilinogen excretion level and δ-aminolevulinic acid were increased- PBG was 42, 7 μmol/dU (N<9) and ALA was 154, 1 μmol/dU (N: 7, 6-53, 4); however no symptoms of porphyria developed.

The mother and child were discharged in good condition on the 9th postoperative day to home care and instructed to avoid activities that put her at risk for dehydration and exhaustion.

The clinical course of porphyria is usually precipitated with hormonal changes associated with pregnancy and menstrual cycle, reduced caloric intake, drugs, infections, alcohol and stress. Both estrogen and progesterone increase the porphyrin precursors (8). Progesterone also increases haem catabolism (10), therefore progesterone is considered more important than oestrogen in precipitating attacks (4). Starvation resulting from nausea and vomiting in hyperemesis gravidarum can also precipitate attack (11). Milo et al reported a case of porphyria in previously healthy pregnant patient precipitated by hyperemesis and metoclopramide treatment (11). Keung et al reported a case of generalized seizure and hypertension occurred after Cesarean section probably related to reduced caloric intake after surgery and pyelonephritis (12). Sudden changes in steroid hormone balance associated with reduced caloric intake make both early pregnancy puerperium as a period of maximal risk for developing an attack (references). Engelhardt et al reported a case of epileptic seizures and status epilepticus in a pregnant patient triggered by hormonal changes and successfully treated with an induced abortion (6). Many medications can induce or worsen porphyria. Usually they are metabolized by liver and may induce the cytochrome P-450 enzymes that require haem (13). Probably unsafe drugs in obstetrical practice include ergot alkaloids, metoclopramide, diclofenac, barbiturates, erythromycin, sulfonamides, lidocain, etc.. Drugs that are not associated with worsening porphyria include oxytocin, bupivacain, petidin, prostigmin, adrenaline, atropine, paracetamol, heparin, etc. (14). Proprofol use in inducing general anesthesia for caesarean section in porphyria patients was first reported by Kantor and Rolbin (15). Drugs we administered postoperative were clexane, petidin, syntocinone and prostigmin (16).

An multidisciplinary approach was needed in this case: anesthesiologist and endocrinologist were consulted and modification of standard postpartal

therapy was made; nausea and vomiting were treated with phenotiazines, pain was relieved with opiates, IV fluid with substantial carbohydrate supply was administered to correct hyponatremia and haematin infusions were made available in case of clinical deterioration . However, in our patient haem therapy was not applied despite increased porphobilinogen and δ-aminolevulinic acid urinary excretion.

The diagnosis of acute porphyria should be considered in all pregnant patients complaining of unexplained abdominal pain. Previous diagnosed cases of porphyria should be closely monitored during pregnancy. Since the diagnosis and management of this life-threatening disease is multidisciplinary, it is imperative to treat such patients in institutions where endocrinologist, neurologist, anaesthesiologist, psychiatrist and cardiologist are available. Porphyric pregnancies remain great challenge for obstetricians.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Puy H, Gouya L, Deybach JC. Porphyrias. Lancet 2010; 375:924–37.
2. Kanaan C, Veille JC, Lakin M. Pregnancy and acute intermittent porphyria. Obstet Gynecol Surv 1989; 44:244–9.
3. Aziz Ibrahim A, Esen UI. Porphyria cutanea tarda in pregnancy: a case report. J Obstet Gynaecol 2004; 24:574–5.
4. Tollanes MC, Aarsand AK, Sandberg S. Excess risk of adverse pregnancy outcomes in women with porphyria: a population-based cohort study. J Inherit Metab Dis 2011; 34:217-23.
5. Cappell MS Hepatic disorders severely affected by pregnancy: medical and obstetric management. Med Clin North Am 2008; 92:739–60.
6. Engelhardt K, Trinka E, Franz G .Refractory status epilepticus due to acute hepatic porphyria in a pregnant woman: induced abortion as the sole therapeutic option? Eur J Neurol 2004; 11:693–7.
7. Jacquemyn Y. Erythropoietic protoporphyria in pregnancy. J Obstet Gynaecol 2003; 23:196.
8. Andersson C, Innala E, Backstrom T. Acute intermittent porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. J Intern Med 2003; 254:176–83.
9. Marsden JT, Rees DC. A retrospective analysis of outcome of pregnancy in patients with acute porphyria. J Inherit Metab Dis 2010; 33:591–6.
10. De Siervi A, Rossetti MV, Parera VE, Mendez M, Varela LS, del Batlle AM. Acute intermittent porphyria: biochemical and clinical analysis in the Argentinean population. Clin Chim Acta 1999; 288:63–71.
11. Milo R, Neuman M, Klein C, Caspi E, Arlazoroff A. Acute intermittent porphyria in pregnancy. Obstet Gynecol 1989; 73:450 -2.
12. Keung Y, Chuahirun T, Cobos E. Acute intermittent porphyria with seizure and paralysis in the puerperium. J Am Board Fam Pract 2000; 13:76-9.
13. Kaupinnen R. Porphyrias. Lancet. 2005; 365:241-52.
14. Brodie MJ, Moore MR, Thompson GG, Goldberg A, Low RA. Pregnancy and the acute porphyries. Br J Obstetr Gynaecol 1977; 84:726-31.
15. Kantor G, Rolbin SH. Acute intermittent porphyria and Caesarean delivery. Can J Anaesth 1992; 39:282-5.
16. Badminton MN, Deybach JC. Treatment of an acute attack of porphyria during pregnancy. Eur J Neurol 2006; 13:668–9.

Intermitentna hepatička porfirija u trudnoći s uspješnim perinatalnim ishodom

Domagoj Vidosavljević[1], Siniša Šijanović[2], Mirjana Rubin[2], Maja Košuta Petrović[2], Kristina Abičić Žuljević[2], Ivana Šimić[3]

[1]Odjel ginekologije i porodništva, Opća bolnica Vukovar, Vukovar; [2]Klinika za ginekologiju i porodništvo, Klinički bolnički centar Osijek, Osijek; [3] Dom zdravlja Đakovo, Đakovo; Hrvatska

SAŽETAK

Porfirije su rijetke metaboličke bolesti uzrokovane defektom enzima biosinteze hema. Slučajevi porfirija u trudnoći su rijetki, a smrtnost kod trudnica u akutnim napadima, prema literaturi, penje se i do 42%. Prikaz slučaja opisuje trudnoću kompliciranu intermitentnom hepatičkom porfirijom s uspješnim perinatalnim ishodom. Naime, mnogi su rizici hepatičke porfirije u trudnoći, pa takve trudnoće predstavljaju izazov za kliničara. Trudnice s prethodno dijagnosticiranom porfirijom treba pomno pratiti tijekom trudnoće, a dijagnozu akutne porfirije treba uzeti u obzir kod u svih trudnica s neobjašnjivim bolovima u abdomenu.

Ključne riječi: porfirija, trudnoća, perinatalni ishod.

CASE REPORT

Traumatic anterior dislocation of the crystalline lens and its surgical management

Sunčica Srećković, Mirjana Janićijević Petrović, Nenad Petrović, Svetlana Jovanović, Svetlana Paunović, Tatjana Šarenac

Ophthalmology Clinic, Clinical Centre of Kragujevac, Serbia

Corresponding author: Sunčica Srećković; Ophthalmology Clinic, Clinical Centre of Kragujevac; Zmaj Jovina 30, 34000 Kragujevac, Serbia; Phone/fax: +381 34 370073; Email: sunce.sun@yahoo.com

Original submission: 19 May 2011; **Revised submission**: 29 August 2011; **Accepted**:

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):123-125

ABSTRACT

This paper reports a case of a 57-year old female who had sustained a blunt ocular trauma resulting in anterior dislocation of the crystalline lens and acute painful visual loss in the left eye. The patient was managed with anterior chamber intracapsular phacoemulsification through a small anterior capsulotomy, pars plana vitrectomy, and surgical iridotomy. Aphakia was corrected by a contact lens. Two months after the surgery, the best corrected visual acuity was 0.9 in the left eye. The vision and retina remained stable in her follow-up examination 1 year later. Anterior dislocation of the crystalline lens can cause severe complications so that dislocated lens should be removed immediately.

Keywords: anterior dislocation, crystalline lens, phacoemulsification, trauma

INTRODUCTION

The causes of crystalline lens dislocation are trauma, spontaneous dislocation, and various hereditary disorders including Marfan syndrome, retinitis pigmentosa and spherophakia (1, 2). Anterior dislocation of the crystalline lens can cause severe complications such as corneal edema, pupillary block glaucoma, and uveitis and recommended immediate surgical treatment (3). On the other hand, there is an increased risk of expulsive hemorrhage during the surgical intervention (2). We are reporting a case of traumatic anterior dislocation of the crystalline lens and the method of its surgical management.

CASE REPORT

A 57-year old female with sudden visual loss and pain in her left eye was admitted to our ophthalmology clinic. She had a history of blunt ocular trauma with a metal lid under pressure on her left eye. The patient's medical and family history was unremarkable. On examination, visual acuity in the right eye was 1.0 and in the left eye it was reduced to counting fingers. The intraocular pressure (IOP), measured by a Goldmann applanation tonometer, was 14 mmHg in the right eye and 55 mmHg in the left eye. Anterior segment examination and dilated fundus examination was unremarkable in her right eye. Anterior segment examination revealed anterior dislocated crystalline lens with blood in anterior chamber, traumatic mydriasis and corneal touch in the left eye (Figure 1). No zonules were seen around the dislocated lens. Fundus examination disclosed vitreous hemorrhage and peripapillary intraretinal hemorrhage. She was initially treated with meditations for controlling IOP and inflammation. Two days after admission a surgery was performed. An ophthalmic viscosurgical device (OVD) was injected

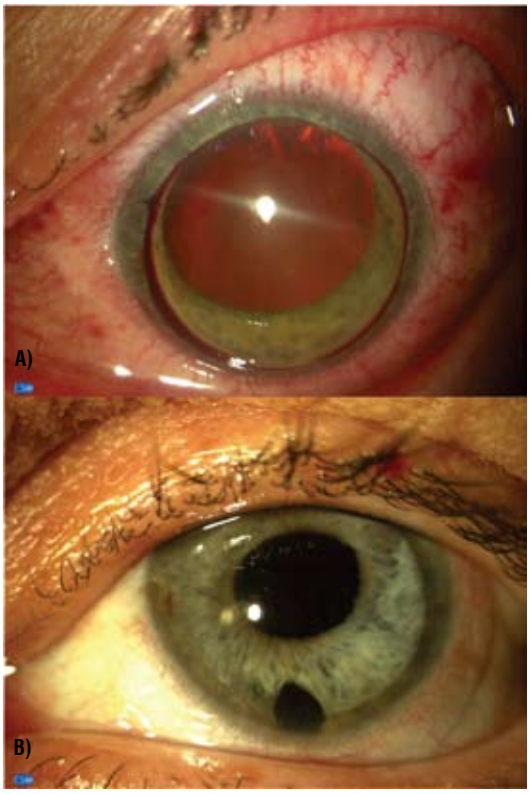


Figure 1. Slit lamp photographs preoperative in the left eye with complete anterior lens dislocation (B) and postoperative with dislocated lens after it was removed and aphakia was corrected by contact lens (A) (Srećković S., 2009).

between cornea and dislocated crystalline lens followed by 2.75 mm incision at 12 o'clock. Using a bent needle, an anterior capsulotomy was made, followed by intracapsular phacoemulsification. Lens capsule and vitreous hemorrhage was surgically removed by pars plana, 20-gauge vitrectomy. Two months after the surgery, aphakia was corrected by a contact lens and the best corrected visual acuity was 0.9 in the left eye (Figure 1). The vision and retina remained stable in her follow-up examination 1 year later (Figure 2).

Lens luxation into the anterior chamber is rare compared with luxation into the vitreous body. The most common cause of crystalline lens dislocation is trauma, with frequency slightly above 50% (1, 2). Hereditary cases have been reported, usually associated with systemic disturbances, such as Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, and some cases of spontaneous luxation (1-6). Therefore, unlike a lens dislocated into the vitreous, an anterior dislocated crystalline lens should always be removed immediately (1). Anterior dislocation of the crystalline lens can cause severe complications such as corneal edema, pupillary block glaucoma, and uveitis (3). In anterior lens dislocations, prolonged contact of the lens with the corneal endothelium can result in permanent decompensation of the cornea (3). We treated the patient successfully, with intracapsular phacoemulsification through a small anterior capsulotomy in the anterior chamber and pars plana vitrectomy. The use of a 2.75 mm incision decreased the risk of expulsive hemorrhage, which can occur during large-incision open chamber surgery. Using an OVD, it is possible to protect endothelial cells during the surgical invasion, resulting in minimal endothelial cell loss and maintenance of corneal clarity. We did not implant any artificial lens because we thought that it would further damage already seriously injured eye. After a year, the best corrected visual acuity was 0.9 in the left eye and retina remained stable. Previous studies recommended the immediate removal of a lens when dislocation is seen into the anterior chamber to prevent severe complications. Jaffe at al suggest an intracapsular extraction through a limbal incision, while Peyman et al recommend vitrectomy with scleral incision (1, 7). Choi et al reported anterior vitrectomy and intercapsular lensectomy with the closed chamber technique. This technique reduces the risk of expulsive hemorrhage with sudden decrease in IOP (2). Seong et al suggest intracapsular phacoemulsification with anterior vitrectomy and scleral-fixated posterior chamber intraocular lens (PC IOL) (8). In patients with subluxated lenses associated with Marfan syndrome, Hirashima et al performed phacoemulsification and iris-fixated PCIOL or phacoemulsification and iris-claw anterior chamber IOL (ACIOL) (9). To correct aphakic patients without capsular support Hara et al.proposed retropupillary fixation of an iris-claw intraocular lens (10).

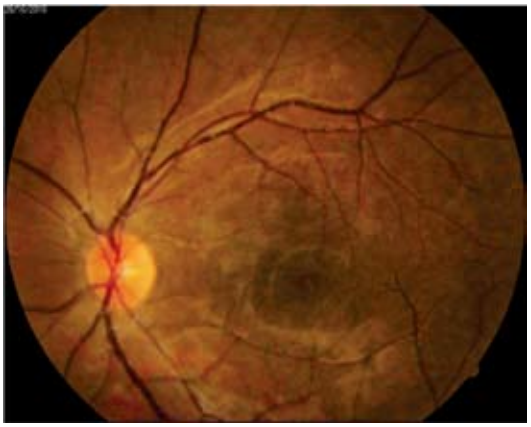


Figure 2. **Fundus of the left eye: follow-up examination one year after vitrectomy showing normal findings** (Srećković S., 2010).

Anterior dislocation of the crystalline lens can cause severe complications, therefore, the dislocated lens should be removed immediately. We believe that the intracapsular phacoemulsification through a small anterior capsulotomy in the anterior chamber is the treatment of choice for anterior dislocated lens.

ACKNOWLEDGEMENT

The authors want to thank to all our colleagues, who takes a part in the examination.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Jaffe NS, Jaffe MS, Jaffe GF. Cataract Surgery and its Complications. 6th ed. St. Louis: Mosby Year Book, 1997, 201-12.
2. Choi DY, Kim JG, Song BJ. Surgical management of crystalline lens dislocation into the anterior chamber with corneal touch and secondary glaucoma. J Cataract Refract Surg. 2004; 30: 718–21.

3. Kawashima M, Kawakita T, Shimazaki J. Complete spontaneous crystalline lens disclocation into the anterior chamber with severe corneal enothelial losss. Cornea 2007; 26: 487–9.
4. Netland KE, Martinez J, LaCour OJ III, Netland PA. Traumatic lens dislocation: a case report. J Emerg Med 1999; 17: 637-639.
5. Kwon YA, Bae SH, Sohn YH. Bilateral spontaneous anterior lens dislocation in a retinitis pigmentosa patient. Korean J Ophthalmol 2007; 21:124-6.
6. Jovanović M, Stefanović I. Spontaneous dislocation of a transparent lens to the anterior chamber-a case report. Srp Arh Celok Lek 2010; 138:486-8.
7. Peyman GA, Raichand M, Goldberg MF, Ritacca D. Management of subluxated and dislocated lenses with the vitrophage. Br J Ophthalmol 1979; 63:771–8.
8. Seong M, Kim MJ, Tchah H. Argon laser iridotomy as a possible cause of anterior dislocation of a crystalline lens. J Cataract Refract Surgery 2009; 35:190-2.
9. Hirashima DE, Soriano ES, Meirelles RL, Alberti GN, Nose W. Outcomes of iris-claw anterior chamber versus iris-fixated foldable intraocular lens in subluxated lens secondary to Marfan syndrome. Ophthalmology 2010;117:1479-85.
10. Hara S, Borkenstein AF, Ehmer A, Auffarth GU. Retropupillary fixation of iris-claw intraocular lens versus transscleral suturing fixation for aphakic eyes without capsular support. J Refract Surg 2011; 30:1-7

Hirurški tretman traumatske dislokacije providnog sočiva u prednju očnu komoru

Sunčica Srećković, Mirjana Janićijević Petrović, Nenad Petrović, Svetlana Jovanović, Svetlana Paunović, Tatjana Šarenac

Klinika za oftalmologiju, Klinički centar Kragujevac, Srbija

SAŽETAK

U radu je prikazan slučaj 57-godišnje žene s akutnim bolnim gubitkom vida i dislokacijom providnog sočiva u prednju očnu komoru nakon kontuzione povrede levog oka. Pacijentkinja je tretirana prednjekomornom intrakapsularnom fakoemulzifikacijom, kroz malu prednju kapsulotomiju, pars plana vitrektomijom i hirurškom iridotomijom. Afakija je korigovana kontaktnim sočivom. Dva meseca nakon operacije, vidna oštrina s korekcijom iznosila je 0.9 na levom oku. Godinu dana od intervencije vidna oštrina i nalaz na retini su stabilni.

Dislokacija providnog sočiva u prednju očnu komoru može uzrokovati ozbiljne komplikacije, pa se dislocirano sočivo treba neodložno ukloniti.

Ključne reči: prednja dislokacija, providno sočivo, fakoemulzifikacija, trauma

CASE REPORT

Acute paroxysmal praecordial pain as a somatosensory elementary partial onset of epileptic seizure

Dragica Vrabec-Matković[1], Duška Šklebar[2], Ivan Šklebar[3], Mislav Klobučić[4], Renata Ivanac Janković[4]

[1]Medical Rehabilitation Hospital Varaždinske Toplice, Varaždinske Toplice, [2]Department of Neurology, [3]Department of Anaesthesiology and Intensive Care, [4]Department of Internal Medicine; Bjelovar General Hospital, Bjelovar; Croatia

Corresponding author: Dragica Vrabec-Matković; Special Medical Rehabilitation Hospital Varaždinske Toplice; Trg slobode 1, 42 223 Varaždinske Toplice, Croatia; Phone: +385 426 30 396; fax.: +385 426 30 827; E-mail: dvmatkovic@yahoo.com

Original submission: 13 May 2011; **Revised submission:** 12 September 2011; **Accepted**: 06 October 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):125-128

ABSTRACT

It presents a 60-year-old female patient with acute paroxysmal intensive pain attacks in the praecordial area that spread to the left hand and were associated with mild transient left hemiparesis, progressing to a myoclonic focal seizure in the region of left abdomen. The diagnostic procedure was interrupted several times by intensive pain attacks, but excluded acute thoracic pathological process, whilst a brain scan found a large, partially necrotic tumour with incipient bleeding and severe oedema subcortically in the right parietal lobe. We are describing a clinical presentation of symptomatic, simple focal, somatosensory epileptic seizure with dominance of intensive pain that progress in myoclonic, somatomotor focal seizure and Todd's Palsy as the first sign of glioblastoma bleeding.

Key words: acute pain, symptomatic partial-onset epilepsy, somatosensory seizure, brain tumour, Todd's Palsy

INTRODUCTION

Intracranial tumours can manifest themselves in different ways, which can generally be divided into three types: patients with changes in mental function, headaches and epileptic seizures, patients with elevated intracranial pressure, and patients with specific intracranial tumour syndromes (1). The occurrence of focal or generalized epilep-

tic seizures is a sign of focal brain damage (2). In different studies, seizures were observed in 20-50% of all patients with brain tumours (3, 4). Pain as an ictal symptom, distinct from other sensory phenomena, is a rare epileptic feature (5-7).

CASE REPORT

A 60-year-old female patient was admitted to the emergency department because of sudden praecordial pain that occurred whilst hand-washing laundry which changed the position of the head and body. She had a sense of a rapid heart rate, a mild weakness of the left arm and left leg instability. She did not vomit, lose consciousness or have headache. The blood pressure was 180/110 mmHg. She received sublingual niphedipine, and because of a suspected stroke, was sent to neurology.

Four days before hospitalization the patient had "a bad feeling in her head" that was not headache, pressure or dizziness. The previous day, she had difficulties with her left leg whilst walking up the stairs, which she associated with previously present problems of lower back pain. She had been on an arbitrary fruit diet with the aim of improving her general condition for the past three months and had lost 6 kg. According to her husband, there was no change in her behaviour, and there was no reported loss of consciousness. She had not used any medication during the previous two months except for a postmenopausal hormone replacement therapy in the form of transdermal patch (estradiol hemihydrate in a dose of 50 micrograms per day).

Two years before she had undegone an appendectomy, twelve years earlier a hysterectomy and an ovariectomy, and twenty-two years earlier she had thyroid surgery. She had recovered from hepatitis A 10 years before with no specific treatment except rest and a dietary regimen. At the age of 28, whilst pregnant, she had a twitch on the left side of the face, and she was treated at a tertiary epilepsy centre with the diagnosis of epileptic seizure (methylphenobarbitone for one year). As she had no symptoms she stopped taking the antiepileptic drugs voluntarily, and she was not subsequently monitored. She has not had any type of head injury.

At admission the patient had considerably less intense praecordial pain than at home, and occasionally she was painless. She was afebrile, blood pressure was 160/90 mmHg, a pulse of about 120/min. She had a praecordial systolic murmur 1-2 /VI, vesicular breathing, expressed pulsations in jugulum, her arms and legs were without oedema, meningeal syndrome tested negative, the right corner of her lip was laid lower and she had a painful left arm with mild weakness. She was not able to stand, had atypical skin plantar response in her left foot, all sensory modalities seemed to be preserved and sphincters were controlled.

During the electrocardiographic recording (ECG), she felt a strong attack of praecordial pain. The patient yelled, cried, had a panicking fear of death and whilst fully conscious she described a spasm in the left part of the chest, under her breast, but there was no visible motor phenomena. During this attack of pain, tachycardia appeared with blood pressure increase. Izosorbide dinitrate was administered sublingually, metamizole intravenously, and the pain was relieved. Considering the severe praecordial pain, the weakness of the left arm and the sudden appearance of pain, differential diagnostics suspected a possible myocardial infarction, dissection of aorta, thoracic disc hernia, pulmonary embolism, stroke development or a possible psychogenic non-epileptic, rather than epileptic attack. A laboratory blood test resulted in normal values, except for a sedimentation rate of 42. During the diagnostic procedure that was interrupted several times because of attacks of intolerable pain, the patient was transferred to coronary care unit for monitoring of the vital functions. The ECG findings, just as the level of serum enzymes, did not show signs of myocardial infarction. Transthoracic echocardiography showed an incomplete diastolic relaxation of the left ventricle and a mild mitral valve back prolapse without regurgitation. Then the patient suffered a repeat attack of strong spastic praecordial pain, but now with myoclonic jerks of musculature of left abdomen. A CT brain scan verified an expansive, partly necrotic formation, localized subcortically in the right parietal lobe, with initial haemorrhage within the necrotic tissue and a huge perifocal oedema with expressed ring imbibitions after the application of contrast agent. Fundus oculi, chest X-ray, abdominal ultrasound, a CT scan of the thorax and carotid Doppler ultrasonogram were normal.

An electroencephalographic report was changed focally (Figure 1). Even before the introduction

of treatment, her left arm weakness recovered spontaneously (Todd's palsy), with a lagging pronation of forearm and dysesthesia of the left side of the body. Diagnostic analysis was completed with findings of the brain MRI that confirmed a solitary expansive process in the right parietal lobe (Figure 2). Operative findings and histopathological analysis confirmed the diagnosis of glioblastoma multiforme. Due to size of the tumour process and the absence of any praecordial pain symptoms, no additional cardiac tests were made during the course of the disease. She had no similar symptoms until the death ten months later.

A brain tumour manifested itself in the patient in the form of a very intense praecordial pain, whilst consciousness was fully preserved. Myoclonic jerks of left abdomen only appeared in the fourth pain attack. Somatosensory attacks are almost always indicative of focal damage in or near the post-rolandic structure of the opposite hemisphere (1, 5). These sensory disturbances are commonly described as numbness, tingling, pricking, shuddering as if receiving an electrical shock or movements of the body, and pain or an impaired sensation of warmth may occur, but this is rare (1, 5-7). The combination of severe pain and postictal weakness (Todd's Palsy) is not common. Todd's Palsy is related to damage in the contralateral hemisphere and the abstraction of the central structure (8-10). Cardiovascular autonomic manifestations of seizures (alterations in heart rate and rhythm, blood pressure, ECG changes and chest pain) are not fully elucidated in their neuroanatomical aspect, but are usually connected with temporal lobe epilepsy (11, 12). The localization of a tumour in right parietal lobe in our patient has coincided with the sensory symptoms in her contralateral body side and the cause of epileptic activity was probably just bleeding in the necrotic glioblastoma. Thirty-two years earlier, during pregnancy, the patient had partial seizures in the left side of her face. Recent advances suggest that oestrogen is not solely endocrine factor that acts inside the hypothalamus and that it is not only involved in reproductive processes (13). An oestrogen can also influence mood, higher cognitive functions, pain mechanisms, fine motor skills and susceptibility to seizures (14, 15). It is possible that epilepsy was induced by hormone activity during the pregnancy of our patient. The question is: is it possible that at that time there was evidence of neuron populations of increased sensitivity and potential malignancy? Did the postmenopausal hormone level and oestrogenic skin patch influence the manifestation of the tumour (16, 17). Or, was it just a coincidence, and a period of thirty-two years was too long to make the connection between these two states?

The clinical presentation of severe praecordial pain and jerks of left part of the abdomen caused by bleeding in a brain tumour is a rare ictal semiology, and the ictal pain is a rare symptom of parietal lobe seizure origin.

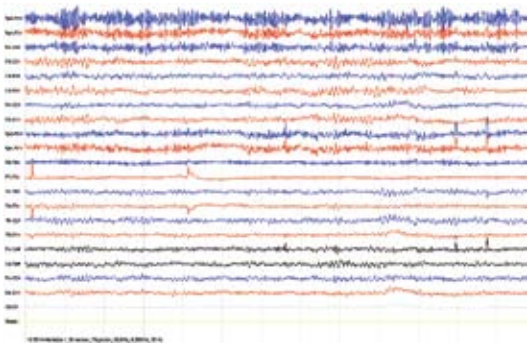


Figure 1. An electroencephalography finding low voltage activity in right temporo- parietal derivations and focal high voltage slow waves (5-7Hz) parieto-occipital left

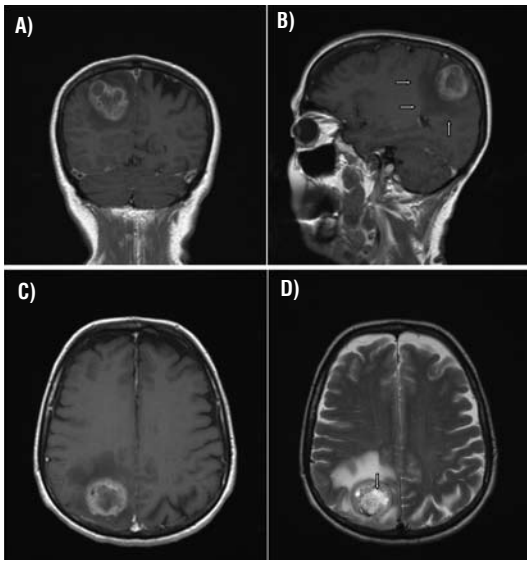


Figure 2. A) Coronal T1-weighted MRI and B) sagittal T1-weighted MR image show right parietal subcortical tumour, size 40x34x33 mm with expressed ring gadolinium imbibitions and deeply spreading oedema (white arrows); C) Axial T1 and D) Axial MRI, T2- weighted image shows extensive perifocal oedema and bleeding in partly necrotic tumour (white arrow) (Vrabec-Matković D., 2006)

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Victor M, Ropper AH. Adams and Victor´s principles of neurology.7th ed. New York: McGraw-Hill, 2001.
2. Rajneesh KF, Binder DK. Tumor-associated epilepsy. Neurosurg Focus 2009; 27:E4.
3. Alajbegović A, Loga N, Alajbegović S, Suljić E. Characteristics of symptomatic epilepsy in patients with brain tumors. Bosn J Basic Med Sci 2009; 9:81-4.
4. Hildebrand J, Lecaille C, Perennes J, Delattre JY. Epilpetic seizures during follow-up of patients treated for primary brain tumors. Neurology 2005; 65:212-5.
5. Scolz J, Vieregge P, Moser A. Central pain as a manifestation of partial epileptic seizures. Pain 1999; 80:445-50.
6. Eschle D, Siegel AM, Wieser HG: Epilepsy With Severe Abdominal Pain. Mayo Clin Proc 2002; 77:1358-60.
7. Noordally O, Mircev D, Luabeya MK. Cerebral arteriovenous malformation mimicking acute coronary syndrome. Acta Neurol Belg 2002; 102:36-8.
8. Binder DK. A history of Todd and his paralysis. Neurosurgery 2004; 54: 486-7.
9. Kellinghaus C, Kotagal P. Lateralizing value of Todd's palsy in patients with epilepsy. Neurology 2004; 62:289–91.
10. Sethi N, Labar D, Torgovnick J, Sethi P, Arsura E, Barliya T, Wasterlain A. Pseudo Todd's palsy in a patient with medically intractable epilepsy. The Internet Journal of Neurology 2009; 11. http://www.ispub.com/journal/the_internet_journal_of_neurology/volume_11_number_2_7/ article/pseudo-todd-s-palsy-in-a-patient-with-medically-intractable-epilepsy.html (10 May 2011)
11. Freeman R. Cardiovascular manifestations of autnomic epilepsy. Clin Auton Res 2006; 6:12-7.
12. Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguière F. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. Cereb Cortex 2002;12:376-85.
13. Chakraborti A, Gulati K, Ray A. Estrogen actions on brain and behaviour: recent insights and future challenges. Rev Neurosci 2007; 18:395-416.
14. Pennell PB. Hormonal aspects of epilepsy. Neurol Clin 2009; 27:941-65.
15. Scharfman HE, MacLusky NJ. The influence of gonadal hormones on neuronal excitability, seizures, and epilepsy in the female. Epilepsia 2006; 47:1423-40.
16. Graf MR, Jia W, Loria RM. The neuro-steroid, 3beta androstene 17alpha diol exibits potent cytotoxic effects on human malignant glioma and lymphoma cells through different programmed cell death pathways. Br J Cancer 2007; 97:619-27.
17. Mhyre AJ, Dorsa DM. Estrogen activates rapid signaling in the brain: role of estrogen receptor alpha and estrogen receptor beta in neurons and glia. Neuroscience 2006; 138: 851- 8.

Akutna paroksizmalna prekordijalna bol kao oblik žarišnog somatosenzornog epileptičkog napada

Dragica Vrabec-Matković[1], Duška Šklebar[2], Ivan Šklebar[3], Mislav Klobučić[4], Renata Ivanac Janković[4]

[1]Specijalna bolnica za medicinsku rehabilitaciju Varaždinske Toplice, [2]Djelatnost za neurologiju, [3]Djelatnost za anesteziologiju i intenzivno liječenje, [4]Djelatnost za unutarnje bolesti; Opća bolnica Bjelovar, Bjelovar; Hrvatska

SAŽETAK

U radu je prikazana 60-godišnja bolesnica s akutnim paroksizmalnim napadima jake prekordijalne boli koja se širila u lijevu ruku i bila povezana s blagom prolaznom lijevostranom hemiparezom, te je progredirala u mioklonizme lijevog hemiabdomena. Dijagnostičkom obradom, koja je prekidana nekoliko puta zbog ataka intenzivnih bolova, isključen je uzrok bolova u grudnom košu, dok je temeljem CT-a mozga otkriven veliki, dijelom nekrotični tumor mozga subkortikalno u desnom parijetalnom režnju s početnim krvarenjem i izraženim edemom. Opisana je klinička prezentacija simptomatskog, jednostavnog žarišnog somatosenzornog epileptičkog napada s izraženom intenzivnom boli, koji je progredirao u miklonički somatomotorni žarišni epileptički napad udružen s Toddovom paralizom kao prvim znakom krvarenja u glioblastom.

Ključne riječi: akutna bol, simptomatska žarišna epilepsija, somatosenzorna epilepsija, tumor mozga, Toddova paraliza

CASE REPORT

Lumboischialgia as the first sign of stomach cancer

Renata Ivanac Janković[1], Duška Šklebar[2], Mislav Klobučić[1], Ivan Šklebar[3], Dragica Vrabec-Matković[4]

[1]Department of Internal Medicine, [2]Department of Neurology, [3]Out-patient Pain Centre; General Hospital Bjelovar, Bjelovar, [4]Special Medical Rehabilitation Hospital Varaždinske Toplice, Varaždinske Toplice; Croatia

Corresponding author: Renata Ivanac Janković; Department of Internal Medicine, Bjelovar General Hospital, Mihanovićeva 8, HR-43000 Bjelovar, Croatia; Phone: +385 98 898 867; fax.: +385 43 279 364; E-mail: renata.ivanac@bj.t-com.hr

Original submission: 27 March 2011; **Revised submission**: 07 June 2011; **Accepted**: 03 August 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):128-130

ABSTRACT

The paper reports on a case of a seventy-three-year-old male patient, whose disease was initially manifested by severe low back pain and lumboischialgia of the right leg as the first and only, and later, the leading symptom of disseminated adenocarcinoma of the stomach. The unusual presentation of stomach cancer confirms the necessity of simultaneous treatment of pain and determination of its etiology. It also indicates the need for re-evaluation of diagnosis when there is no favorable clinical effect of applied therapy.
Keywords: lumboischialgia-differential diagnosis, stomach cancer-symptoms, pain

INTRODUCTION

Lumboischialgia is a radicular pain in the distribution of the sciatic nerve as a result of lumbar disc degeneration or herniation of one or more lumbar-sacral intervertebral discs (1). In cases of atypical clinical presentation or inadequate response to therapy procedures other possible causes of pain (tumours, infections or injuries) could be considered. Stomach cancer often has no symptoms in early stages and also there is no single symptom that exactly pinpoints stomach cancer.

CASE REPORT

A 73-year-old man was admitted to the Department of Internal Medicine due to extensive hematomas of the body, microangiopathic haemolytic anaemia and lumboischialgia. The illness began with severe low back pain and right lumboischialgia one month ago. Patient had good appetite, constant body weight and there was no nausea or vomiting. Stool and urine were normal. At physical examination he was afebrile, auscultatory findings of heart and lungs were normal, and blood pressure was 120/65 mmHg. There were no enlarged lymph nodes. Abdomen examination discovered mild suprapubic pain on palpation without organomegaly. Neurological examination showed a positive Lasègue sign and absent myotactic reflexes on both legs and inability to walk on his toes and heels. Abnormal laboratory findings were: red blood cells (RBC) 1.95 $x10^{12}$/L , haemoglobin (Hb) 57 g/L, mean cell volume (MCV) 89.9 fL, platelets 36 $x10^{9}$/L, prothrombin time (PT) 0.48, fibrinogen 1.5 g/L, bilirubin 68.9 mikromol/L, lactate dehydrogenase (LDH) 849 U/L, alkaline phosphatase (AKP) 1377 U/L, and the tumour marker CA 19-9 was ten times higher than the reference value. The patient was treated with transfusion of blood and fresh frozen plasma, the infusion of crystalloid and analgesia. Gastroscopy disclosed tumour infiltration of the lesser curvature of stomach, and bone marrow examination found metastatic adenocarcinoma. Abdomen CT disclosed multiple osteolytic metastases of the thoracic and lumbar spine, the callosity of stomach wall and two enlarged lymph nodes para-aortic and aorto-caval left. Few days later the patient was treated with palliative irradiation of the spine to reduce pain along the right sciatic nerve, which remains the leading symptom of disseminated malignant disease of stomach.

Pain is a major symptom in many medical conditions and the most common reason for physician consultation. Low back pain with or without radiation down the lower limb is a common state that usually occurs as a result of lumbar disc degeneration and disc herniation (1). While primary neoplasia in the lumbar spine is rare, metastatic disease is relatively common (2). Problem with stomach cancer is that it is often detected late because of its presentations with nonspecific symptoms and at the time of diagnosis the disease is often advanced and treatment options are limited (3,4). In this case we showed that stomach cancer, although rare, is a cause of metastases to bones. At the time of diagnosis the stomach cancer is localized only in 10-20% of cases, and can be treated surgically, with subsequent implementation of chemotherapy and radiotherapy. The inoperable cancer in the advanced stage can be treated with radiotherapy and chemotherapy. Methods of palliative treatment with chemotherapy / radiotherapy remain for metastatic disease including adequate analgesia (5). In our patient differential diagnosis considered thrombotic thrombocytopenic purpura, vasculitis, bone marrow tumour infiltration, polyneuropathy, and comorbidity of these disorders with low back pain as a result of lumbar spine degeneration.

Stomach cancer is often detected in advanced stage, because patients usually do not have symptoms in early stages. This case demonstrates that first presentation of stomach cancer can be, although less common than in breast, kidney, thyroid, prostate and bronchial cancer, with bone metastases (4). This report of unusual first presentation of adenocarcinoma of the stomach with lumboishialgia also confirms the necessity of simultaneous treatment

of pain and determination of its etiology.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Stafford MA, Peng P, Hill DA. Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management. Br J Anaesth 2007; 99:461-73.
2. Reddi AH, Roodman D, Freeman C, Mohla S. Mechanisms of tumor metastasis to the bone: challenges and opportunities. J Bone Miner Res 2003;18:190-4.
3. Brenner H, Rothenbacher D, Arndt V. Epidemiology of stomach cancer. Methods Mol Biol. 2009; 472:467-77.
4. Hussain S, Chui S. Gastric carcinoma presenting with extensive bone metastases and marrow infiltration causing extradural spinal haemorrhage. Br J Radiol 2006; 79:261-3.
5. Kelsen DP. Adjuvant and neoadjuvant therapy for gastric cancer. Semin Oncol 1996; 23:379-89.

Lumboishialgija kao prvi simptom karcinoma želuca

Renata Ivanac Janković[1], Duška Šklebar[2], Mislav Klobučić[1], Ivan Šklebar[3], Dragica Vrabec-Matković[4]

[1]Djelatnost za interne bolesti, [2]Djelatnost za neurologiju, [3]Ambulanta za bol; Opća bolnica Bjelovar; [4]Specijalna bolnica za medicinsku rehabilitaciju Varaždinske Toplice; Hrvatska

SAŽETAK

U radu je prikazan slučaj 73-godišnjeg muškarca čija se bolest inicijalno manifestirala jakim bolovima u lumbalnom području, sa širenjem boli duž desne noge kao jedinim, a kasnije vodećim simptomom diseminiranog adenokarcinoma želuca. Opis slučaja neuobičajene prve prezentacije adenokarcinoma želuca lumboishijalgijom, potvrđuje neophodnost istovremenog liječenja boli i utvrđivanja njenog izvorišta radi pravovremenog kauzalnog liječenja. Također ukazuje na potrebu reevaluacije dijagnoze i učinjenih laboratorijskih i radioloških nalaza kada se u bolesnika, unatoč terapiji, ne postiže povoljan klinički učinak.

Ključne riječi: lumboishijalgija - diferencijalna dijagnoza, karcinom želuca - diferencijalna dijagnoza, liječenje boli

CASE REPORT

Benign blue naevus of the lungs

Biserka Pigac[1], Svjetlana Marić [2], Silvija Mašić[1]

[1]Pathology, Citology and Forensic Medicine Unit, Varaždin General Hospital, Varaždin, [2]Department of Medical Biology, Medical Faculty, University Josip Juraj Strossmayer, Osijek; Croatia

Corresponding author: Biserka Pigac; Pathology, Citology and Forensic Medicine Unit; Varaždin General Hospital; Ivana Meštrovića bb, 42 000 Varaždin, Croatia;

Phone: +385 42 393 564; fax: +385 42 393 566;

E-mail: biserka.pigac@vz.t-com.hr

Original submission: 15 April 2011; **Revised submission**: 06 June 2011; **Accepted**: 15 July 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):130-132

ABSTRACT

Blue naevus is a dark blue, gray or black lesion consisted of dermal melanocytes and usually found on face, scalp, or on the dorsum of hands and feet. Two well defined histologic and clinical variants, designated as "common" and "cellular", have been recognised. An unusual case of accidentally detected common blue naevus of the lungs has been reported. The specimen of lung tissue was taken during autopsy of a 62-year old woman who died of myocardial infarction. Microscopic analysis revealed the area containing melanocytes filled with melanin pigment.

Key words: blue naevus, benign, lungs

INTRODUCTION

Blue naevus was first reported in 1906 by Tiesche (1). It is considered to be a benign melanocytic lesion that usually manifests as an asymptomatic, slate-blue or blue-black, smooth-surfaced macule or papule (1). Although blue naevi are considered to be tumors of the skin, their presence has been noticed in other sites. Examples of some unusual locations are prostate, uterine cervix, genital mucosa, lymph node capsule, conjunctiva, Mullerian tract, brain, lungs, oral mucosa, sclera, spermatic cord, pulmonary hilus, orbit, maxillary sinus and breast (2-4).

This paper has presented an uncommon case of accidentally detected common blue naevus of the lungs.

CASE REPORT

An autopsy was performed in a 62-year-old woman who suffered from chronic heart failure, arterial hypertension, diabetes mellitus, and she died of the consequences of myocardial infarction. On that occasion, during the procedure, specimen of the lung tissue for pathohistological analysis was taken.

Tissue specimen consisted of a small dark red piece of lung tissue measuring 2x1x1 cm. Routine H&E and immunohistochemical staining were performed. The following antibodies were used: S-100 protein, HMB-45 and vimentin to demonstrate the immunoreactivity of tumor cells.

Macroscopically, the tissue specimen represented oedematose, dark red pulmonary material without any visible signs pointing to blue naevus. A more detailed analysis of the tissue followed by microscopic examination of the biopsy specimen. Pulmonary oedema and congestion of the tissue were dominant pathologic elements, but careful examination revealed also small microscopic areas of the tumor tissue consisted of spindle- shaped melanocytes containing plenty of brownish pigment melanin in their cytoplasm (Figure1). Entwined bundles of collagen fibres between melanocytes were also observed. The tumor appeared to be benign common blue naevus. Immunohistochemically, tumor cells expressed immunoreactivity for S-100 protein (Figure 2A), HMB-45 (Figure 2B) and vimentin (Figure 2C).

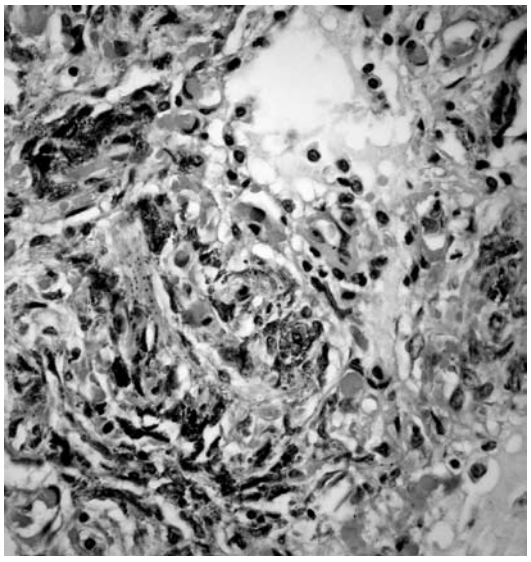


Figure 1. Benign blue naevus of the lungs. Pulmonary oedema and tissue congestion with pigmented lesion consisting of spindle-shaped melanocytes containing brownish pigment melanin in their cytoplasm and discrete collagen bundles between melanocytes (H&E staining, x **40**); (Pigac B., 2011)

The most common definitions of blue naevus describe it as benign melanocytic tumor that classically occurs in the skin, appears bluish macroscopically due to the presence of deep intradermal pigment melanin viewed through skin and as an entity that carries low potential for malignant transformation (2). Blue naevus could appear at any age, but usually in the third decade or later in life (1). They could be described as pigmented lesions consisting of melanocytes that can appear in diverse forms: dendritic, spindle-shaped, oval-shaped, or polyhedral (5). Clinically and histologically, two types of blue naevus can be distinguished: the common and the cellular blue naevus (5). Common blue naevus clinically has been presented as black blue papules placed in any site of the body (6). Cellular blue naevus tend to be larger than 1 cm in diameter and present themselves as dark blue black nodules (6). They are commonly found on the buttocks, sacral region, dorsum of hands and feet (6). The presence of blue nevus appears to be clinically benign in most cases, but rare cases of malignant melanoma have been reported to ocur in cellular blue nevus (6). The origin of all types of blue naevus is believed to be the consequence of neural crest melanocytes dermal arrest during embryonal migration which results in their failure to reach the epidermis (3,4). Collections of melanocytes can be found in fetal dermis, but they involute during later gestation (7). The recognizable blue color of the naevus is due to the presence of melanin and the Tyndall effect (preferential absorption of long wavelengths of light by pigment melanin and the scattering of shorter wavelengths, representing the blue part of the spectrum) (7). In this presented case the naevus was macroscopically undetectable, but after microscopic analysis it could be described as a common blue naevus appearing in lung parenchyma.

This case has risen pathologic curiosity because of the unusual location of this clinically and histologically benign entity and point to possible confusion of this benign condition to malignant pigmented lesions, such as melanoma, and other health threatening conflictive lesions, such as atypical blue nevus, locally aggressive blue nevus, congenital giant melanocytic nevus with nodular growth, melanocytic dermal tumor, malignant blue naevus (5).

In conclusion, the presence of blue naevus in unusual and unexpected locations is rare, but should be considered as differential diagnosis in order to avoid unnecessary traumatization of the

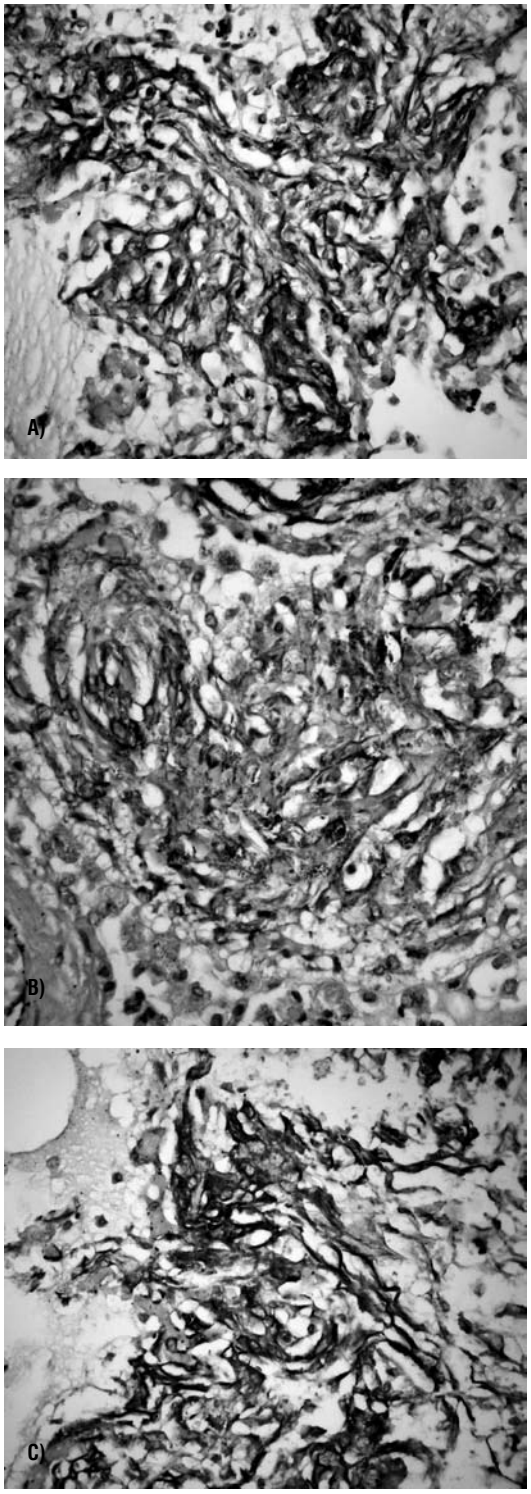


Figure 2. Benign blue naevus of the lungs. Immunohistochemical staining of lung tissue and pigmented lesion by A) S-100 protein (spindle- shaped melanocytes of the pigmented lesion demonstrate strong immunoreactivity for S-100 protein (S-100, x 40) **B) by HMB-45. (spindle- shaped melanocytes of the pigmented lesion demonstrate medium level of immunoreactivity for HMB- 45** (HMB- 45, x 40); **C) by VIMENTIN (spindle- shaped melanocytes of the pigmented lesion demonstrate strong immunoreactivity for VIMENTIN** (VIMENTIN, x 40) (Pigac B., 2011).

patient in case of benign lesion and to prevent significant morbidity, metastatic disease and death in the case of pigmented malignant lesion that clinically appears to be benign.

FUNDING

This work was supported by grants 219-2192382-2386 and 219-2192382-2426 from the Croatian Ministry of Science, Education and Sport.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Soares Marques YM, De Deus Moura de Lima M, Raitz R, Dos Santos Pinto D, Jr, Orsini Cantanhede Machado de Sousa S. Blue nevus: report of a case. *Gen Dent 2009; 57:e1-e3.*
2. Berman EL, Shields CL, Sagoo MS, Eagle RC, Jr, Shields JA. Multifocal blue nevus of the conjunctiva. Surv Ophthalmol 2008; 53:41-9.
3. Craddock KJ, Bandarchi B, Khalifa MA. Blue nevi of the Mullerian tract: case series and the review of the literature. J Low Genit Tract Dis 2007; 11:284-9.
4. Goldman RL. Blue naevus of lymph node capsule: report of a unique case. Histopathology. 1981; 5:445-50.
5. Gonzales-Campora R, Galera-Davidson H, Vazquez-Ramirez FJ, Diaz-Cano S. Blue nevus: classical types and new related entities. A differential diagnostic review. Pathol Res Pract 1994; 190:627-35.
6. Mittal RR, Gupta R, Sethi PS. Cellular blue naevus. Indian J Dermatol Venereol Leprol 2001; 67:200-1.
7. Craft N, Fox LP, Goldsmith LA. VisualDx. Essential adult dermatology. Philadelphia: Lippincott Williams & Wilkins, 2010.

Dobroćudni plavi nevus pluća

Biserka Pigac[1], Svjetlana Marić [2], Silvija Mašić[1]

[1]Odsjek za patologiju, citologiju i sudsku medicinu, Opća bolnica Varaždin, Varaždin; [2]Odsjek za medicinsku biologiju, Medicinski fakultet, Sveučilište "Josip Juraj Strossmayer", Osijek; Hrvatska

SAŽETAK

Plavi nevus je tamnoplava, siva ili crna tvorba, sastavljena od dermalnih melanocita. Lice, vlasište, te dorzum šaka i stopala, najčešće su lokacije na kojima nalazimo plavi nevus. Poznata su dva dobro definirana histološka i klinička tipa ovog nevusa: "obični" i "celularni". U ovom radu predstavljamo neobičan slučaj jednog slučajno otkrivenog običnog plavog nevusa pluća. Prilikom obdukcije 62-godišnje žene, umrle od infarkta miokarda, uzet je uzorak tkiva pluća, te je provedena mikroskopska analiza. Rezultati analize pokazali su areal tkiva sastavljen od melanocita ispunjenih pigmentom melaninom.

Ključne riječi: plavi nevus, dobroćudan, pluća

Tematic issue:

The hip arthroplasty – orthopedic surgery of the 20th century

EDITORIAL

Hip arthroplasty – orthopedic surgery of the 20th century

This thematic volume of *Medicinski Glasnik* entitled ''Hip arthroplasty – orthopedic surgery of the 20th century" intends to illustrate general and regional experience with hip arthroplasty.

Total hip arthroplasty has revolutionized the treatment of a wide range of pathological conditions resulting in hip dysfunction and has brought about significant improvements in restoring functional ability and quality of life in affected patients. Sixty years have elapsed since the first hip arthroplasty was performed in our region (1, 2). With contributions from orthopedic surgeons, anesthesiologists, radiologists and cardiologists, this thematic volume features several interesting articles that focus on current concepts and also provide comprehensive reviews of several topics and controversial areas in the field.

One of the articles focuses on anesthesiological issues in total hip arthroplasty. In this systematic literature review, the author presents guidelines for the procedures before, during and after total hip arthroplasty, as well as for the implementation of thromboprophylaxis.

Another article deals with a clinically important and somewhat controversial issue of diagnosis and management of infected total hip arthroplasty (THA). Infection is one of the most common underlying reasons for early THA failure and has become the leading reason for THA revision. The article reviews evidence supporting various diagnostic modalities and treatment approaches.

Further included articles address the possibility of performing multi-slice computed tomography in patients with implanted hip endoprosthesis, comparisons between mini-invasive and standard surgical techniques in hip arthroplasty, and the effects of long-term high-dose corticosteroid treatment in heart transplant recipients on hip pathology.

The review paper "Total hip arthroplasty - yesterday and today" reviews the general and regional history of THA as well as the contemporary attitudes towards the factors affecting endoprosthesis survival.

Taken together, this thematic volume clearly illustrates that THA is no longer simply ''an orthopedic issue", but rather a multidiciplinary one. It also illustrates a great progress that has occurred over the past decades resulting in considerable improvement of outcomes. The most important elements are related to greater application of biotechnological sciences resulting in production of implants with improved biological, structural and biomechanical properties. Progress has been made also in the field of surgical techniques, where the mini-invasive surgery and computer-assisted surgery have a potential to provide nearly ideal implant placement with a consequent faster and better rehabilitation.

Clearly, further professional training and improvement of all elements of the process, as well as development of implant registries, should help us in the creation of strategies with optimal cost-effectiveness and long-term outcomes. One should not fail to mention that in achieving this goal a multidisciplinary approach is a must and that achieving this goal would undoubtedly convey benefits for the entire community.

It has been a privilege for me to serve as a guest editor for this thematic issue. I have enjoyed working with my esteemed colleagues in putting it together and have learned a lot from them in the process. With gratitude for their valuable contributions, I hope that this issue will add knowledge to the area of arthroplasty and will help practicing doctors involved in the process of diagnosis, treatment and rehabilitation of patients with total hip arthroplasty.

Prof. Robert Kolundžić, MD, PhD

Guest Editor

Prof. Selma Uzunović-Kamberović, MD, MA, PhD

Editor-in-Chief

Medicinski Glasnik

REFERENCES

1. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. Lancet 2007; 370:1508-1519.
2. Orlić D. Aloartroplastika kuka. Zagreb: Medicinski fakultet Sveučilišta u Zagrebu; 1986.

REVIEW

History and factors of survival of total hip arthroplasty

[1]Robert Kolundžić, [2]Vladimir Trkulja, [3]Dubravko Orlić

[1]Clinic for Traumatology, Clinical Hospital Center „Sestre Milosrdnice“, [2]Zagreb University School of Medicine, [3]Croatian Medical Association; Zagreb, Croatia

ABSTRACT

Since the 1960s total hip arthroplasty (THA) has represented one of the greatest accomplishments in orthopedic surgery. It improves the functionality, working ability and quality of life of patients with non-functional hip joint due to various reasons. This article reviews general and regional history of THA, current knowledge and concepts regarding the long-term outcomes of the procedure and emphasizes the need for establishing national (and international) THA registries as an essential way of gathering data critical for decision making in daily practice as well as in defining national healthcare policies in respect to arthroplasty procedures.

Key words: arthroplasty, long-term outcomes, registry

Corresponding author:
Robert Kolundžić
Clinic for Traumatology,
Clinical Hospital “Sestre Milosrdnice”
Draškovićeva 19, 10000 Zagreb, Croatia
Phone: +385 1 46 79 194;
fax.: +385 1 46 79 100
E-mail: robert.kolundzic@zg.t-com.hr

Original submission:
01 November 2011;
Accepted:
29 November 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):136-142

INTRODUCTION

Since the 1960s, total hip arthroplasty (THA) has represented one of the largest accomplishments in orthopedic surgery (1). It decreases pain and improves mobility of a damaged joint thus enabling a dramatic improvement in quality of life (2,3). Endoprosthetic surgery has seen huge improvements over the last decades, not only regarding the hip joint but also with respect to all other larger joints or parts of the skeletal system, with very good results (2,4,5).

HISTORY OF TOTAL HIP ARTHROPLASTY

The first interpositional arthroplasty was probably performed by Rehn in Freiburg, Germany, at the beginning of the 1930s, but did not prove successful (6). It was not until Smith-Petersen (1933) and his use of „cup" plastic as a shaped interpositum between the cup and the head of the femur that better and more lasting results were achieved, which are today considered precursors of modern resurfacing prosthesis (7).

The first total hip arthroplasty was performed by Wiles in London in 1938. The implant consisted of two steel components and this event has been considered the first precursor of modern procedures (1). Since that time, all endoprotheses in such procedures were implanted without the use of cement and had dentures and holes which strengthened the fixation through bones growing into the prothesis (1). Sir John Charnley revolutionized the treatment of degeneratively changed hips by introducing three large novelties: polymethylmethacrylate that served as bone cement, i.e., as a material for fixation of endoprothesis of the hip joint, polyethylene as the material for making components that have a bearing surface, and the new construction of endoprothesis of the hip joint entitled "low friction torque arthroplasty". In a large number of studies with long term follow-up (over 20 years), the Charnley prothesis/technique enabled survival longer than 10 years in about 80% of the cases (8,9,10).

As late as 10 years since the introduction of bone cement in practice, McKee explained why bone cement improved the success rate. The success was attributed to the fact that by using the bone cement the contact surface between the implant and the bone was increased (11). In this way McKee pointed out the key learning of endoprosthetic fixation: the distribution of forces among surfaces of the endoprothesis and the bone.

The history of non-cemented endoprotheses of the hip joint started in the early 1960s when Svash, in the USSR, first started implanting them, but their use was soon abandoned due to a large number of early instabilities (12). In fact, it can be concluded that Ring, in 1964, was the first one to implant a reasonably successful non-cemented total hip endoprothesis, a metal-metal endoprothesis in which the acetabular component was fixated by screwing the other ending into the bone (13). At the end of the 1970s, the use of non-cemented endoprotheses started in the metal-plastic combination such as, for example, the Endler model, which was also, with time, abandoned due to early instabilities.

A revolutionary event in the development of the hip joint endoprosthetics, particularly for non-cemented endoprotheses, is the construction of the implant that could be wedged into the bone bed, the so called *press-fit* fixation, the founder of which was Wagner (14).

The history of resurfacing endoprotheses of the hip joint started with Sir John Charnley who was the first who tried to include the restoration of the surface of the head and acetabulum by a teflon surface. This attempt, however, failed due to the development of aseptic necrosis of the femoral head and the bone reaction to the material that was used for building the acetabular component (8, 9,15).

The history of implanting endoprotheses of the hip joint in the regions of former Yugoslavia and the surrounding region, started at the Clinic for Orthopedics in Zagreb, the head of which, at that time, was Prof. Ferdo Grospić, MD, PhD. Thus, in 1949 Vitalium cup plastic was implanted and, in 1960, the first partial endoprothesis was used (Austin Mooreu). Owing to Prof. Albert Starzzyk, MD, PhD and Academic Ivo Ruszkowski, MD, PhD, total hip arthroplasty was introduced in 1970, in particular the non-cemented endoprothesis of the Ring model, and its clinical use began at the Clinic for Orthopedics of the Clinical Center Zagreb, which covered this entire region (16).

It is also very important to note the pioneering endeavor in the construction and clinical application of the Croatian model of the femoral component of endoprothesis. This was the ROM endoprothesis of the hip joint whose name comes

from the initials of the surnames of its inventors – Ruszkowski – Orlić – Muftić (2, 17). It was a cement mono-block endoprothesis in which the head was manufactured as fixated on the head of endoprothesis.

SURVIVAL OF TOTAL HIP ARTHROPLASTY

Total hip arthroplasty, a procedure almost unknown until half a century ago, soon became a routine procedure applied by many orthopedicians, who simply liked their patients being impressed by the fast immediate success. It was precisely that fast success of the hip joint endoprotheses implantation that, in a way, masked certain risks associated with the procedure, particularly the complications that resulted in a shortened survival of the artificial joint (18). Generally, one could say that, regardless of the endoprosthesis type, modern endoprostheses achieve ten-year survival rate at around or above 95%, twelve-year survival rate at around or above 84%, fifteen-year survival rate of around 66% and around 50% of the implanted endoprostheses survive for 18 years or longer (19).
THA is a large orthopedic procedure which, as any other operative procedure, brings a possibility of certain complications, one being the development of aseptic instability of the implant. In part, the risk of developing this complication is related to the scale of damage to the hip, bone quality, musculature quality and type of the surgery, comorbidity and, naturally, surgeon's experience, however not even an experienced surgeon's work is completely without complications. Traditionally, the investigation of risk factors of aseptic instability of THA has been focused on demographic factors (age, sex), biomechanical factors (body mass index, acetabular inclination) and morbidity factors (reasons for prothesis implantation), and factors related to material characteristics (cemented, non-cemented, resurfacing) and surgeon's skill. Bearing everything in mind, all these factors explain only a small part of the variability of occurrence of aseptic instability of THA suggesting that the key factors determining whether (and when) it will develop in a particular patient are still to a large extent unknown. It is a common opinion that there are „patient-dependent factors", which are not demographical or biomechanical, that predominantly determine one's individual ''inclination" towards the development of aseptic instability (20-22).

Endoprostetic materials as factors influencing development of the particle disease

Many alloys, plastic materials and, lately, ceramics used to construct hip endoprotheses in theory guarantee almost unlimited durability of endoprothesis by the virtue of their minimal friction coefficients. However, the fact is that the issue of endoprosthetic durability in clinical practice obtains a completely new dimension. In reality, building materials are one of the causes of instability of endoprotheses developed due to aseptic inflammation. In this respect, one has to point out high-molecular polyethylene, which has been extensively used for building the entire acetabular part of cemeted endoprotheses or components of the uncemented acetabular parts, as a prototypical particle-releasing material. The released particles induce local aseptic inflammation that eventually leads to THA instability. Considering the inducing role of the released particles and the relationship between the amount of released particles and the intensity of the process, it has been named "particle disease" (23). Today, a number of endoprosthetic models and materials are in use and for many of them we do not have sufficient data as to reliably estimate the associated risk of aseptic instability (24). Still, it is known that the risk of aseptic instability is lower for all forms of hydroxyapatite-coated non-cemented endoprotheses than for cemented endoprotheses (be it femoral or acetabular parts), and that the highest risk is associated with uncoated non-cemented endoprotheses (25). However, despite the differences in its incidence, aseptic instability occurs with all materials and endoprothesis types, whereby the same mechanisms/mediators are in place (22).

Demographic factors

Analyses of THA registries in the Scandinavian countries (tens of thousands of prostheses) (25,26) focused on long-term survival with aseptic instability as the endpoint, demonstrated both younger age at THA and female sex as independent negative predictors – the risk of aseptic instability is significantly higher in patients younger than 55 years (than in those older than 55 years) and in women (than in man), but the "effect" of sex is marginal.

Biomechanical factors

The level of physical activity and body mass index influence the forces that affect the endoprothesis, thus they are considered as biomechanical factors. Another potentially important factor would be the constructional one that is, the biomechanical features of the endoprothesis (26). A large number of endoprothetic models are available, that differ significantly with respect to constructional details. There is no data based on which one could conclude about potential differences in aseptic instability occurrence that would be attributable to the constructional features. There is also no data that would indicate that the surgical procedures that are sometimes necessary in addition to the endoprothesis implantation (acetabuloplasty or trochanter osteotomy), and which change the biomechanical situation of the hip joint, affect the occurrence of aseptic instability. On the other hand, the inclination angle of the acetabulum achieved at endoprothesis implantation significantly influences the occurrence of aseptic instability. Namely, the goal is to achieve an angle of 45 degrees, whereby a discrepancy of +/- 5 degrees is tolerated. Unfavorable inclination angle of the acetablumum due to a bad biomechanics of the joint itself, and consequently larger friction between the constituting part of the endoprothesis, increases the risk of aseptic instability (27, 28). Unfortunately, it has been shown that aseptic instability occurs also with a favorable inclination angle (40-50 degrees) (19).

Exceeding body mass (body mass index, BMI, >25 and particularly >30) is a classical factor that contributes to (over)burdening of the skeletal-muscular system, and also of the hip endoprothesis. However, the research of the influence of BMI on the occurrence of aseptic instability is related with certain problems. Namely, in this kind of research the outcome of interest is time elapsed until the occurrence of event (instability) and patients are followed-up for a long period of time (e.g., 10 years or longer). Data are typically analyzed with the assumption of the "constant hazard" - it is assumed that the risk associated with a certain factor is constant over time (for example, age at the time of surgery, type of endoprothesis, gender, disease leading to the need for endoprothesis, etc.). Body mass index can change significantly over time. In the literature, there is practically no study in which BMI has been considered as a time-dependent variable. It is therefore difficult to realistically assess the influence of this factor on the occurrence of aseptic instability. In a study conducted over a shorter period of time, body mass index >30 at the time of the implantation of endoprothesis was identified as a negative factor for the endoprothesis survival (29). It should be noted, however, that aseptic instability occurs also in patients with a permanent physiological body mass index.

Other factors

Based on the analysis of around 54,000 endoprotheses from the Norwegian THA registry (30), the risk of aseptic instability is higher in patients with developmental hip anomalies than in those in which THA was indicated for other reasons (e.g., primary osteoarthritis, aseptic necrosis of the femoral head, injuries etc).

Based on the analysis of around 32,000 endoprotheses (cemented and non-cemented) from the Norwegian THA registry (31, 32), more experienced surgeons (measured by a number of procedures annually) need less time for the implantation of endoprothesis than less experienced surgeons. Independent of the age and gender of a patient, the type of endoprohesis or disease that led to the need for endoprothesis, the risk of aseptic instability is higher in patients treated by less experienced surgeons. The risk of aseptic instability is greater if the operations last longer than the average of 90 minutes. Also, the risk is greater if the operation lasts shorter than 50 minutes.

For quite some time, it has been a common opinion that there are "patient-dependent factors", which are not demographic, (co)morbidity or biomechanical, that significantly determine the individual „inclination" towards the development of aseptic instability of THA (33-35). Namely, large interindividual differences have been noticed in the intensity of the inflammatory process which results in aseptic instability for a given type of prothesis, for the amount of loose particles, demographic, (co)morbidity and biomechanical features and the „skill of the surgeon". During the last 7-8 years, the concept has arisen which assumes that this „unexplained part of the indivi-

dual inclination“ is genetically defined. Humoral and cellular mediators of inflammation in particle disease are well known, and it is assumed that mutations in the coding genes that reflect on their expression and/or function could explain the individual inclination towards a more severe inflammation under the given circumstances. Indeed, up to-date, several mutations in genes encoding cytokines involved in “particle disease” have been shown associated with a higher risk of aseptic instability of THA. Even though this field is at its beginnings, it is clear that it has a potential to improve the individual approach to each patient targeted at achieving even better results of hip joint arthroplasty.

THE HIP ARTHROPLASTY REGISTER

During the 1970s the construction of hip joint endoprotheses flourished, and thus constructions were made that also had discouraging results, with loosening rates of up to 30% three years after implantations and even 60% within six years from the implantation. Due to such situations, in the early 1980s the first national registries of hip joint endoprotheses were established in the Scandinavian countries (36).

The purpose of Scandinavian registries of implanted endoprotheses is to keep records of all implanted endoprotheses, their type, patient characteristics, reason for implantation, complications, reoperations, endoprothesis survival rate, operative technique, operation duration and operating surgeon (33,37). These data provide a variety of information which is very useful when choosing endoprothesis. For example, an early analysis, conducted in Norway (37), showed that during a four-year period in that country over 1,000 endoprotheses were implanted (of various designs) with bad outcomes. Following such defeating numbers, the majority of endoprothesis that had been used were withdrawn from the market. During 1990s, and mainly during the beginning of this century, almost every EU country introduced a register of endoprothesis of hip and knee, all under the umbrella of the European Association of Orthopaedcians and Traumatologists (EFORT) which is developing a European Arthroplasty Register (EAR) and which will be the coordinator of all national endoprothesis registries (38).

In conclusion, THA has revolutionized the treatment of a whole range of conditions that result in hip dysfunction, bringing about a significant improvement in functional ability and quality of life of the affected patients, and it has been proclaimed the orthopedic surgical procedure of the 20th century. However, further improvements are possible and necessary considering construction and materials of the hip joint endoprothesis, development of surgical techniques, particularly in the segment of reoperations, and better understanding of individual factors leading to endoprosthesis rejection. Establishing national (and international) endoprothesis registries is another important goal as they could provide data that could change the way of thinking of practicing surgeons, professional associations and health administration when it comes to questions of choice of the prosthesis type, patient selection, operating techniques and other procedures.

ACKNOWLEDGEMENTS

This paper was written as part of a project under the sponsorship of the Ministry of Health and Social Welfare and Sports of the Republic of Croatia, under the number 098-0000000-3530 ‘’Molecular Basis of Aseptic Instability of Hip Joint Endoprothesis“.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

Literature:

1. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. Lancet 2007; 370:1508-19.
2. Orlić D. Aloartroplastika kuka. Zagreb: Medicinski fakultet Sveučilišta u Zagrebu, 1986.
3. Rorabeck C H, Bourne R B, Laupacis A, Feeny D, Wong C, Tugwell P, Leslie K, Bullas R. A double-blind studyof 250 cases comparing cemented with cementless total hip arthroplasty. Cost-effectiveness and its impact on health-related quality of life. Clin Orthop 1994; 298:156-64.
4. Chang R W, Pellisier J M, Hazen G B. A cost-effectiveness analysis of total hip arthroplasty for osteoarthritis of the hip. JAMA 1996; 275:858-65.

5. Furnes A, Lie S A, Havelin L I, Engesaeter L B, Vollset S E. The economic impact of failures in total hip replacement surgery: 28,997 cases from the Norwegian Arthroplasty Register, 1987-1993. Acta Orthop Scand 1996; 67:115-21.
6. Rehn E. Zur Wiederherstellungschirurgie der Gelenke. Arch Klin Chir 1934; 180:395.
7. Smith-Petersen MN. The classic: evolution of mould arthroplasty of the hip joint. J Bone Joint Surg 1948; 30B:L59.
8. Charnley J. Arthroplasty of the hip: a new operation. Lancet 1961; 1:1129–32.
9. Havelin LI, Vollset SE, Engesaeter LB. Revision for aseptic loosining of uncemented cups in 4325 primary total hip prostheses. Acta Orthop Scand 1995; 66:494-500.
10. Morscher EW, Hefti A, Aebi U. Severe osteolysis after third-body wear due to hydroxyapatite particles from acetabular cup coating. J Bone Joint Surg Br 1998; 80:267-72.
11. McKee GK. Development of total prosthetic replacement of the hip. Clin Orthop 1970; 72:85.
12. Sivash KM. The development of a total metal prosthesis for the hip joint from a partial joint replacement. Reconstr Surg Traumatol 1969; 11:53.
13. Ring PA. Complete replacement arthroplasty of the hip by the Ring prosthesis. J Bone Joint Surg Br 1968; 50:720.
14. Morscher E. Experiences, requirements and development of cement-free hip endoprostheses. Orthopäde. 1987;16:185-96.
15. Bannister GC. Total Hip Replacement – which type? Curr Orthop 1993; 7:165.
16. Ruszkowski I, Pećina M. Aloplastičke zamjene zglobova. U: Spomenica u povodu 50. obljetnice rada katedre za ortopediju (1922.-1972.). Medicinski fakultet Sveučilišta u Zagrebu, 1973.
17. Muftić O, Orlić D, Ruszkowski I. Croatian model of hip joint endoprosthesis. Periodicum Biologorum 2002; 104:281-5.
18. Kolundžić R, Orlić D, Trkulja V, Pavelić K, Gall Trošelj K. Single nucleotide polymorphisms in the interleukin-6 (IL-6) gene promoter, tumor necrosis factor-α (TNF-α) gene promoter and transforming growth factor-β1 (TGF-β1) gene signal sequence as predictors of time to onset of aseptic loosening after total hip arthroplasty – a preliminary study. J Orthop Sci 2006; 11:592-600.
19. Kolundžić R, Šulentić M, Smerdelj M, Orlić D, Trkulja V. Stability of Endler cementless polyethylene acetabular cup: long-term follow-up. Croat Med J 2005; 46:261-7.
20. Wilkinson JM, Wilson AG, Stockley I i sur. Variation in the TNF gene promoter and risk of osteolysis after total hip arthroplasty. J Bone Miner Res 2003;18:1995-2001.
21. Kolundžić R, Orlić D. Bolesti sitnih stranih čestica – aseptička nestabilnost totalne endoproteze zgloba kuka. Liječ Vjesn 2008; 130:16-20.
22. Kolundžić R, Trkulja V, Orlić D. New insights into aseptic loosening of the total hip arthroplasty: an emerging role of genetics and proteomic. In: Aoi T, Toshida A. Hip Replacement: Approaches, Complications and Effectiveness. New York: Nova Science Publishers; 2009.
23. Gallo J, Kaminek P, Ticha V, Rihakova P, Ditmar R. Particle disease. A comprehensive theory of periprosthetic osteolysis: a review. Biomed Papers 2002; 146:21-28.
24. Morrey BF. Instability after total hip arthroplasty. OCNA 1992; 23:237-48.
25. Aamodt A, Nordsletten L, Havelin LI, Indrekvam K, Utvag SE, Hviding K. Documentation of hip prostheses used in Norway: a critical review of the literature from 1996-2000. Acta Orthop Scand 2004; 75:663-76.
26. Eskelinen A, Remes V, Helenius I, Pulkkinen P, Nevalainen J, Paavolainen P. Total hip arthroplasty for primary osteoarthrosis in younger patients in the Finnish arthroplasty register. Acta Orthop 2005; 76:28-41.
27. Schulitz K P, Dustmann H O. Komplikationen der Totalendoprothese. Arch Orthop Unfallchir 1976; 85:33-50.
28. Malchau H, Herberts P, Eisler T, Garellick G, Soderman P. The Swedish total hip replacement register. J Bone Joint Surg (Am) 2002; 84 (Suppl 2):2-20.
29. Smith PN, Ling RSM, Taylor R. The influence of weight-bearing on the measurement of polyethylene wear in THA. J Bone Joint Surg (Br) 1999; 81:259-65.
30. Kordelle J, Starker M. Migration analysis of cemented Muller polyethylene acetabular cups versus cementfree Zweymuller screw-attached acetabular cups. Z Orthop Ihre Grenzgeb 2000; 138:46-51.
31. Smabrekke A, Espehaug B, Havelin LI, Furnes O. Operating time and survival of primary total hip replacements. An analysis of 31745 primary cemented and uncemented total hip replacements from local hospitals reported to the Norwegian Arthroplasty Register 1987-2001. Acta Ortop Scand 2004; 75:524-32.
32. Eskelinen A, Remes V, Helenius I, Pulkkinen P, Nevalainen J, Paavolainen P. Uncemented total hip arthroplasty for primary osteoarthritis in young patients: a mid- to long-term follow-up study from the Finnish Arthroplasty Register. Acta Orthop 2006; 77:57-70.
33. Furnes O, Lie SA, Espehaug B, Vollset SE, Engesaeter LB, Havelin LI. Hip diseas and the prognosis of total hip replacements. A review of 53698 primary total hip replacements reported to the Norweigian arthroplasty register 1987-99. J Bone Joint Surg (Br) 2001; 83:579-86.
34. Puolakka TJS, Pajamäkil KJJ, Halonen PJ, Pulkkinen PO, Paavolainen P, Nevalainen JK. The Finnish Arthroplasty Register Report of the hip register. Acta Orthop Scand 2001; 72: 433–41.
35. Archibeck MJ, Jacobs JJ, Roebuck KA, Glant TT. The basic science of periprosthetic osteolysis. Instr Course Lect 2001; 50:185-95.
36. Paavolainen P, Hamalainen M, Mustonen H, Slatis P. Registration of arthroplasties in Finland. A nationwide prospective project. Acta Orthop Scand Suppl 1991; 241:27-30.
37. Havelin L I, Engesaeter L B, Espehaug B, Furnes O, Lie S A, Vollset S E. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. Acta Orthop Scand 2000; 71:337-53.
38. European Arthroplasty Register. http://www.ear.efort.org/ (29/11/11)

Povijest i čimbenici preživljavanja umjetnog zgloba kuka

[1]Robert Kolundžić, [2]Vladimir Trkulja, [3]Dubravko Orlić

[1]Klinički bolnički centar „Sestre milosrdnice“, [2]Medicinski fakultet Sveučilišta u Zagrebu, [3]Hrvatski liječnički zbor; Zagreb, Hrvatska

SAŽETAK

Primjena totalne endoproteze zgloba kuka, od 60-tih godina prošlog stoljeća pa do danas, predstavlja jedno od najvećih dostignuća ortopedske kirurgije. Ugradnjom totalne endoproteze zgloba kuka poboljšava se funkcionalnost, radna sposobnost i kvaliteta života bolesnika u kojih je zglob kuka nefunkcionalan uslijed različitih uzroka. Ovaj rad prikazuje globalnu i regionalnu povijest primjene totalnih endoproteza zgloba kuka, moderna saznanja i koncepte vezane za dugoročne ishode zahvata, te naglašava potrebu uspostavljanja nacionalnih i međunarodnih registara totalnih endoproteza zgloba kuka kao temeljnih izvora informacija kritičnih za odlučivanje u svakodnevnoj praksi, ali na razini kreiranja nacionalnih politika u zdravstvu.

Ključne riječi: totalna endoproteza zgloba kuka, dugoročni ishodi, registar

REVIEW

Anesthesia for hip replacement surgery

Branko Tripković

Department of Orthopedic Surgery, School of Medicine, University of Zagreb, Croatia

ABSTRACT

Hip replacement surgery is a common and effective procedure for the relief of pain and loss of function. The number of procedures is increasing and great interest is shown for the manner of outcome improvement following hip replacement surgery. Last decade (2001-2010) is declared as the Bone and Joint Decade and has been characterized by many innovations in hip replacement surgery including minimally invasive technique but also by improvements in anesthetic technique. However there is no consensus about most appropriate anesthetic and analgesic techniques to use. Total hip replacement is procedure characterized by great perioperative disturbances including cardiovascular complications, high incidence of thromboembolic complications, possible significant perioperative blood loss, possible bone cement effect and high level of postoperative pain. Anesthetic assessment of patients include preoperative preparations, intraoperative and postoperative care. Most important factors determining outcome of patients include preoperative assessment and planning in order to minimize potential anesthetic problems, optimize co-morbidity and provide the most appropriate anesthetic for the patient.

In this article all problems of preoperative assessment are discussed. The recent data of advantages of regional anesthetic technique are outlined. All the problems of intraoperative course and how to avoid them are presented. The possible techniques of postoperative pain therapy are also presented. The importance of thromboprophylaxis is outlined and recent guidelines for thromboprophylaxis are given including recommendations for new antithrombotic drugs. Our recommendation is to always prepare a patient for this procedure, analyse preoperative status, choose optimal anesthetic technique, provide thromboprophylaxis and multimodal pain therapy according to accepted guidelines.

Key words: anesthesia, hip replacement, regional anesthesia, thromboprophylaxis, pain therapy

Corresponding author:
Branko Tripković
Department of Orthopedic Surgery,
School of Medicine, University of Zagreb
Šalata 6, 1000 Zagreb, Croatia
Phone: +385 1 2368 986;
fax.: +385 1 2379 913;
E-mail: branko.tripkovic@zg.t-com.hr

Original submission:
19 August 2011;
Accepted:
03 October 2011.

INTRODUCTION

Total hip replacement (THR) surgery has become routine procedure with increasing number being performed each year all around world. Since its introduction in the 1960s total hip replacement has been a standard treatment for patients with osteoarthritis providing significant improvement in physical status and health. Hip replacement surgery is associated with many conditions and complications of which the anesthetist must be aware and many investigations are performed to design optimal conditions for this procedure (1).

Current surveys from the United States and Europe report continued growth in the use of THRs from the 1990s to early 2000. Current projections for the United States suggest that from 2005 to 2030 the number of THRs will increase by 174 %, to nearly 600.000 procedures per year (2). Similar situation is in many other countries as a result of increasing number of people in the age over 65 years. Most patients scheduled for THR are elderly, and commonly have associated medical problems like heart disease or coexisting organ dysfunction that can compromise their outcome after the procedure. In a study performed in the UK it is estimated that in patients undergoing primary hip replacement 63% were the American Society of Anesthesiologists (ASA) grade 2, 14% were grade 3 or worse, and this figure rose to 59% and 26% for revision procedures(3). In order to optimize perioperative course in these patients it is very important to recognize all perioperative problems with patients and perform anesthesia procedures to minimize perioperative risks and complications.

PREOPERATIVE CONSIDERATIONS

Problems in multiple systems are common because most patients are elderly (4). Preoperative assessment and planning should minimize potential anesthetic problems, optimize co-morbidity and provide the most appropriate anesthetic for the patient (5). All patients should be assessed preoperatively two to three weeks before the scheduled procedure and meticulous preoperative assessment must be performed. However, the elective nature of the surgery allows enough time for a thorough work-up, and effective treatment can be initiated if necessary (6). Assessing patients preoperatively includes a detailed history, a physical examination and any indicated laboratory tests. Investigations of cardiovascular and respiratory system, liver and renal function, musculoskeletal and airway status are important. A detailed history of drugs used and allergy should be taken (6).

Standard preoperative laboratory tests include full blood count or hemoglobin level, electrolytes (potassium, sodium), blood glucose level, urea, creatinine, liver enzymes, clotting studies, urinalysis (1).

Problems with cardiovascular system are common in elderly population and typically include hyperthension, ischaemic heart disease, presence of arrhythmias and the congestive heart failure (4). In all patients electrocardiograph (ECG) should be performed routinely. Patients who have ECG evidence of ischaemia or left ventircular hypertrophy require echocardiogram prior to surgery. Patients with systolic murmur also necessitate echocardiography. The most important findings of echocardiograms are value of ejection fraction (EF), which determines cardiac risk preoperatively and possible presence of aortic stenosis (7). Aortic stenosis is more prevalent in elderly patients and is very important to recognize stage of stenosis preoperatively because it will influence the choice of anesthesia (spinal anesthesia is contraindicated in patients with severe aortic stenosis) (8). ECG changes like atrioventicular (AV), right or left bundle branch block necessitate hours of monitoring of cardiac function (Holter) to recognize possible severe conduction problems (9). After all cardiac investigations are performed and if current management is deemed inadequate the cardiologist's assessment is often necessary.

Although a chest roentgenogram provides a baseline, and rarely may detect some unsuspected disease, it is routinely used in elderly patients (10). For checking respiratory system arterial blood gassed and lung function tests can be undertaken. Pulmonary fibrosis may be present as a consequence of rheumatoid arthritis or as a side effect of drugs (e.g. methotrexate) (11). In elderly patients renal function can be affected due to decreased glomerular filtration rate and effects of drugs (e.g. NSAIDs) so urea, serum creatinin and alectrolytes are investigated.

In preoperative assessment musculosceletal and airway status are investigated. Rheumatoid arthritis may affect the cervical spine resulting in atlanto-axial subluxation (12). A potential difficult airway may be anticipated due to reduced neck extension and poor mouth opening. Many

patients are scheduled for regional (spinal) anesthesia and lumbar spine should be examined. If difficult or impossible performing of spinal anesthesia is estimated, lumbar spine radiographs are recommended (13).

The detailed drug history is always taken because multi-pharmacy is common in elderly. Elderly patients may be taking many drugs. Some patients do not know what drugs or how much was taken so consultation with family physician is often helpful. Biochemical abnormalities may be present (diuretics) and possible interactions with anesthetic agents should be considered (14). Warfarin, NSAIDs, beta blockers and angiotensin-converting enzyme inhibitors are commonly prescribed in this age group. These are important when considering regional anesthetic techniques and preoperative cardiovascular performance.(1,6,15).

ANAESTHETIC TECHNIQUE

Total hip replacement surgery can be performed under general, spinal or epidural anesthesia, and a combination of techniques is often used (16). The type of anesthesia should be determined at preoperative anesthetic assessment. Spinal anesthesia is the most commonly used technique, usually in combination with intravenous sedation (6, 16). Epidural blockade or a lumbar plexus block are also widely used, alone or in combination with general anesthesia (6, 16). There are many advantages of regional anesthesia: reduced intraoperative blood loss and reduced requirement for blood transfusion, reduced incidence of postoperative deep vein thrombosis and pulmonary embolism (due to a sympathectomy-induced increase in blood flow and antagonism of the hypercoagulable state), improved postoperative analgesia (especially if a spinal or epidural catheters are used), improved outcome of surgery and anesthesia, reduction in the effects of general anesthesia and systemic opioid analgesia on pulmonary function (basal atelectasis, hypoxaemia and pulmonary infection) and reduced incidence of postoperative nausea and vomiting (1, 6,16, 17). It is also important that in patients with rheumatoid arthritis the need for endotracheal intubation is avoided and potential difficult airway is prevented (12).

During the regional anesthetic technique supplemental oxygen (3-4 L/min) via nasal mask should be administered (6, 17). Sedation may be necessary for uncomfortable patient positioning or prolonged procedures. This can be achieved by intermittent boluses of midazolam (0.5 – 1 mg increments) or by target-controlled infusion of propofol (6, 16).

In some patients regional anesthesia is contraindicated (severe aortic stenosis), impossible to perform (Mb Bechterew) or is strongly refused by patients (6, 18). All these problems are usually recognized during preoperative anesthetic assessment and the operation is performed under general anesthesia (6, 19). Both laryngeal mask airways and endotracheal tubes can be used for airway maintenance. An endotracheal tube is preferred if there is limited access to the airway or if the patient has a history of gastroesophageal regurgitation (1,6). Laryngeal mask airways have been in use for the last 20 years and are very useful for patients with ankylosans spondylitis in whom endotracheal intubation is often impossible (20). Before the introduction of laryngeal mask in clinical practice in many of these patients fiberooptic assistance was necessary or even in some cases tracheothomy was performed to ensure airway management.(1,6)

There are many advantages of regional anesthesia for patients scheduled for THR but there is still debate in literature whether the regional anesthesia improves outcome after THR. In review article published in the British Journal of Anesthesia in 2009 randomized controlled trials were included. According to these trials there is reduction in blood loss and a need for transfusion, postoperative pain, morphine consumption and nausea and vomiting. But there is no difference regarding duration of surgery and length of hospital stay. Mortality, cardiovascular morbidity and deep venous thrombosis and pulmonary embolism are also reduced but the number of patients included in randomized controlled trials is too small and further investigations are needed (21,22).

INTRAOPERATIVE CONSIDERATIONS

Traditionally two units of cross-matched blood should be available. Premedication is given orally like diazepam 5 to 10 mg, or midazolam orally or intramuscular (1,6). Before the procedure intravenous access with a large bore (14 or 16 G) cannula and a standard non-invasive monitoring (ECG, pulse oximetry and non-invasive blood pressure monitoring) should be established (6). In

patients with significant co-morbidity or if undergoing a joint revision procedure an arterial line and central pressure venous catheter may be used for continuous intravascular monitoring (6). Preoperative antibiotic prophylaxis is routinely given intravenously immediately before the induction of anesthesia (e.g. cefazolin 1 g) (23, 24).

Total hip arthroplasty surgery is normally carried out in supine or lateral decubitus position and attention to the position on the table is important (6,25). Care must be taken to support patients and to cushion them from any potential pressure effects and avoid overextension or flexion of joints (especially neck in patients with rheumatoid arthritis) (12). Pressure areas should be particularly avoided in elderly because of delicate condition of the skin and subcutaneous tissue (25).

All patients should be fully monitored with blood pressure, pulse oximetry and ECG. Capnography, inspired oxygen, volatile agents analysis and airway pressure monitoring are indicated for general anesthesia. The blood pressure cuff should be placed on the upper arm to avoid inaccurate readings (1,6).

The duration of the procedure is usually between 1 and 2 hours after introduction of cementless endoprothesis (there in no waste time needed for cement application), but in some patients hypothermia can occur (3, 6). Haemostatic mechanisms are reduced with age, therefore temperature haemostasis is important (6). Heat loss can be significant because of anesthesia induced peripheral vasodilatation (spinal anesthesia cause pharmacology sympathectomy), large wound surface area, high-flow laminar circulation systems, major fluid shifts. Hypothermia may cause poor wound healing and cardiovascular dysfunction. Warmed intravenous fluids and a hot air warming device are desirable. In poor condition patients temperature monitoring can be used. Some surgeons oppose to hot air warming devices because of theoretical risk of wound infection but there has been no investigation of this problem (26).

Patient positioned laterally may become restless and uncomfortable because of pain arising from the dependent shoulder. Intermittent midazolam, titrated in 1 mg increments, may be used but often causes intraoperative disorientation and confusion resulting in patient movement. Increasingly popular is a target-controlled infusion of propofol. As sedation deepens, airway obstruction or snoring may occur. This is seldom a problem in lateral position, but some supine patients may require a nasopharyngeal airway (3,6,16).

There is possibility of significant blood loss. The average blood loss in THR ranges from 300 to 1000 mL intraoperatively and rises to total of 1500 mL in 24 hours postoperatively (27). Blood transfusion is relatively uncommon during surgery in patients with an adequate preoperative Hb. Intraoperative blood loss is in correlation with systolic blood pressure. Many methods are popular for decreasing blood pressure and blood loss: regional (spinal or epidural) anesthesia and deliberate hypotension with many drugs (inhaled anesthetics, vasodilatatory drugs like sodium nitroprusside, nitroglycerin, prostaglandins, calcium channel blockade) (29). Some antifibrinolytics drugs like tranexamic acid, epsilon-aminocaproic acid and aprotinin have all been used in the last 20 years and have resulted in significant decreases in the need for transfusion (30). Unfortunately, aprotinin was recently implicated in thrombosis and has been removed from use (31). Intraoperative transfusion is seldom needed but careful fluid balance is essential because compensatory mechanism are disturbed during anesthesia (especially in elderly) (6). The elderly commonly have coexisting heart disease and as a consequence arterial oxygen carrying capacity and coronary perfusing pressure both should be maintained (6,16). Cell savers are increasingly used as a safer alternative to alogeneic blood transfusion, but their use is financially viable only in revision hip procedures (32).

CEMENT REACTIONS

Although the proportion of uncemented procedures has appeared to increase in recent years, cemented THR is unlikely to be completely supplanted by uncemented arthroplasty (33). If cemented protheses are used, bone cement implantation syndrome (BCIS) may occur (34). Under the pressure from cement (methylmathacrylate - MMA) implantation, a microembolic shower of blood, fat and platelet aggregates can enter venous circulations. This can cause potentially fatal complications when the circulations debris enters the pulmonary circulation because of an increased pulmonary shunt, pulmonary hypertension and reduced ventricular ejection. The subsequent

hypotension may be insufficient for coronary perfusion. The main clinical signs are: hypoxemia, hypotension, dysrhythmias and cardiovascular collapse. A degree of intravenous fluid loading prior to cementing can help minimize these effects and further fluids, boluses of vasopressors (ephedrine) and supplemental oxygen may be required to restore hemodynamic stability (35).

Bone cement implantation syndrome (BCIS) is poorly understood. It is an important cause of intraoperative mortality and morbidity in patients undergoing cemented hip arthroplasty and may be seen postoperatively in a milder form causing hypoxia and confusion (36). Many workers have demonstrated emboli in the heart using transoesophageal echocardiogaphy (37). Post mortem examination performed after intraoperative deaths confirm the presence of marrow, fat, bone emboli and MMA microparticles (38). In addition to simple mechanical obstruction of the pulmonary circulation there are several possible mechanism causing an increase in pulmonary vascular resistance (PVR). The embolism material may release vasoactive or proinflammatory substances that directly increase PVR such as thrombin and tissue thromboplastin. Potential causes are also histamine release and complement activation (39).

The incidence of BCIS is underestimated because of lack of standard definition. Grade 1 of BCIS include moderate hypoxia (SpO_2 <94%) and hypotension (fall in blood pressure > 20%), in Grade 2 severe hypoxia (SpO_2 <88%) and hypotension (fall in blood pressure > 40%), in Grade 3 cardiovascular collapse requiring cardiopulmonaly reanimation (CPR) is present (34). The incidence of Grade 1 and 2 is between 5 and 30% (34). The true incidence of cardiac arrest secondary of BCIS is unknown. The largest study which covered 38 488 hip arthroplasties was published in 1999 and reported 23 intraoperative deaths in 23 077 patients receiving cemented arthroplasty. There were no intraoperative deaths in 15 411 uncemented arthroplasty (38).

In order to protect patients from BCIS medullary lavage before, insertion of cement has been a standard method in cemented THR. With lavage of femoral canal significant reduction of microemboli and mediators is achieved and there is no mediator induced vasoconstriction or mechanical obstruction of pulmonary vasculature and the incidence of BSIC is low (40).

THROMBOPROPHYLAXIS

Following joint replacement venous thromboembolism is a major cause of deaths. Among all surgical procedures the incidence of deep venous thrombosis and pulmonary embolism is highest after joint replacement because of Virchow's triad: endotelial wall damage (intraoperative damage with surgical instruments), venous stasis (patients with THR are bed rest for 24 to 48 hours postoperatively) and surgical induced procoagulant conditions (41).

Without thromboprophylaxis the prevalence of deep venous thrombosis is over 50% after total knee or hip replacement surgery (42). The incidence of calf deep venous thrombosis (DVT) is 40%-80%, proximal DVT 10%-20%, clinical pulmonary embolism (PE) 4%-10%, fatal PE 0.2%-5% (42). Improvement in patient outcomes when regional anesthesia techniques are used is due to the attenuation of the hypercoagulable response and the associated reduction in the frequency of thromboembolism (43). However, this effect is insufficient as the sole method of thromboprophylaxis. In orthopedic patients thromboprophylaxis should be administered preoperatively (42).

There are many recommendations how to perform thromboprophylaxis. The most popular are ACCP (American College of Chest Phycians) recommendations, but there are also ESA (European Society of Anesthesia) recommendations and national recommendations (44). For example, the initial recommendations presented by ACCP in 1986 stated that patients undergoing hip arthroplasty receive dextran, adjusted dose standard heparin (approximately 3500 U every 8 hours), warfarin (started 48 hours preoperatively to achieve a prothrombin time (PT) 1.25 – 1.5 times baseline), or dextran plus intermittent pneumatic compression (45). The duration of thromboprophylaxis is continued after hospital discharge for a total of 10 to 35 days (45, 46).

The ACCP guidelines are widely recognized as a practice standard for VTE prevention and treatment, and have been regularly updated throughout recent decades. The most recent version, issued in 2009, is formally known as the 8th ACCP Conference on Antithrombotic and Thrombolytic Therapy (47).

Strategies to reduce the thromboembolic risk include a combination of regional anesthesia,

anticoagulant drugs, thromboembolic disease stocking or pneumatic leg compression devices and early mobilization (47). It is common practice to administer low molecular-weight heparin (LMWH) e.g. 20 – 40 mg enoxaparin, subcutaneously, once a day, starting on the evening before surgery. (16, 47)

In recent years new drugs have been introduced in clinical practice: fondaparinux (parenterally administered indirect inhibitor of factor Xa) and new perorally anticoagulants (rivaroxaban - an orally active direct factor Xa inhibitor and dabigatran which is factor II inhibitor). Their benefits include administration once a day and no need for laboratory testing of effects because of predictable pharmacokinetic profile (48).

REGIONAL ANESTHESIA AND THROMBOPROPHYLAXIS

The combination of regional anesthesia and thromboprophylaxis is the standard for THR surgery (6, 16). Unfortunately, serious complications like perispinal hematoma can occur after spinal or epidural anesthesia performed in patients receiving thromboprophylaxis (49). Although rare, the seriousness of this complication mandates very cautious use of antithrombotic medications in patients having neuraxial blockade (6, 16). In a review of the literature for the period between 1906 and 1994, 61 cases of spinal hematoma associated with epidural or spinal anesthesia have been reported (49). Great importance of spinal hematoma was recognized after the approval of low molecular weight heparins for clinical use (50). Low molecular weight heparins (LMWH) have been in use in Europe since 1989 and in the USA since 1993. In 1997, only 4 years after the release of LMWH for general use in the USA in May 1993, a series of 43 patients who had developed perispinal hematoma after receiving the LMWH enoxaparin concurrently with spinal or epidural anesthesia have been reported (51). Many of these patients suffered neurologic impairment, including permanent paralysis, despite decompressive laminectomy. The median age was 78 years (28-90), and 78 % of patients were women. Concomitant antiplatelet therapy was present in several cases. Nearly 90% of these complications occurred in patients receiving enoxaparin as prophylaxis after primarily total knee or hip replacement. (52) Many of these events occurred when LMWH was administered intraoperatively or early postoperatively to patients undergoing continuous epidural anesthesia and analgesia (52). At same time 10 cases of spinal hematoma have been reported in Europe (51). The possible explanation for this apparent difference in incidence in Europe may be a result of a difference in dose and dose schedule. For example, in Europe the recommended dose of enoxaparin is 40 mg daily initiated 12 hours preoperatively while in the USA it is 30 mg twice daily (52). The predisposing factors also include the presence of an underlying haemostatic disorder, traumatic needle or catheter insertion, repeated insertion attempts or blood return, time of catheter insertion or removal, use of continuous epidural catheters, administration of medications known to increase bleeding (53). Manufacturers of LMWHs subsequently added a boxed warning to the prescribing information, alerting clinicians to this potential effect. However, it became clear that at least some of these outcomes resulted from lack of attention to timing of the neuraxial anesthesia relative to the dose of LMWH, traumatic needle placement, and catheter removal during therapeutic levels of anticoagulation (54).

In response to these serious complications the American Society of Regional Anesthesia and Pain Medicine (ASRA) held three Consensus Conferences on Regional Anesthesia and Anticoagulation where recommendations how to perform regional anesthesia in patients receiving anticoagulation drugs were achieved. These recommendations were published in the Journal of Regional Anesthesia and Pain Medicine. According to the recommendations, spinal anesthesia can be performed 2-4 hours after a dose of unfractioned heparin; 10-12 hours after a dose of LMWH and in patients receiving warfarin only if international ratio (INR) is < 1.5.(1,15,16)

New antithrombotic drugs are given postoperativelay 4 – 8 hours after the wound closure, so there is a minimal risk for spinal hematoma (50).

ANALGESIA AFTER TOTAL HIP REPLACEMENT SURGERY

Improvements in pain management techniques in the last decade have had a major impact on the practice of THR (55). Although there are numerous treatment options for postoperative pain, a gold standard has not been established (56). Ner-

ve blocks and neuraxial techniques provide better postoperative pain relief than systemic opioids alone (57). A multimodal approach in which two or more drugs acting on different receptors in the pain pathway are used in combination (58).

Single dose spinal opioids provide superior analgesia compared with systemic opioids, but may also be associated with adverse effects (59). The onset and duration is determined by lipophilicity of drug. Lipophilic opioids such as fentanyl provide rapid onset of analgesia, and rapid clearence and resolution. Hydrophilic opioids such as morphine have longer duration of action but are associated with greater frequency of side effects (the most serious is respiratory depression) (60).

Recommendations for analgesia after THR include several points. Non-steroidal anti-inflammatory drugs (NSAID) or selective COX-2 inhibitors are recommended because they decrease pain and supplementary analgesics consumption (they should be given in combination with strong opioids for high intensity pain); but it should be remembered that their use in patients with impairment of platelet function and gastric ulcers carries a significant risk of bleeding complications (61). Systemic strong opioids are recommended for high-intensity pain. The dose depends on the patient's weight and age. With method of intravenous boluses the standard dose is 1-2 mg morphine to a total of 10-20 mg, but the most popular is patient controlled analgesia - PCA during first 24 hours following surgery with special designed pumps and determined basal rate - usually 2 mg/h, demand dose 1-2 mg and lockout period of 20 minutes. (62). Paracetamol is recommended as a baseline treatment for all pain intensities because it decreases supplementary analgesic requirements (63). Femoral nerve blocks (3-in-1) are recommended or posterior lumbar plexus blocks which have a greater efficacy (64). Continuous epidural analgesia with local anesthetic and opioids is recommended for cardiopulmonaly risk patients because of decrease in cardiopulmonary morbidity associated with epidural analgesia (continuous infusion permits analgesia to be more precisely titrated but is also associated with technical failures, hypotension, ileus and urinary retention) (65).

Patient controlled analgesia (PCA) or on-demand opioids combined with paracetamol and NSAID's provide effective analgesia and is a widely used method. The benefits of using NSAID's in elderly must be balanced against increased risk of impaired renal function (66,67).

In recent years some new methods have been under investigation like intraoperative periarticular injection of steroid and opioid containing local anesthetic in all the soft tissues surrounding the hip. The steroids prevent local inflammation, and morphine stimulates opiate receptors in the joint with less systemic effects (68). There are also changes in multimodal analgesia. New drugs are added to combination of analgesics with different mechanism of action. The use of antihyperalgesics such as gabapentin and N-methyl-D-aspartate receptor antagonist ketamine in combination with different analgesics is under investigation (69). For any combination of analgesics it should be remembered that, if strong opioids are used, patient monitoring is necessary because there is danger of serious respiratory depression especially in elderly patients.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Miller RD. Anesthesia. 5th ed. New York-Edinburg-London-Philadelphia: Churchill Livingstone, 2000.
2. Kurtz S, Mowat F, Ong K. Prevalence of primary and revision total hip arthorplasty in the United States from 2005 to 2030. J Bone Joint Surg Am 2007; 89:780-5.
3. Edge G, Fennelly M. Trauma and orthopaedic anesthesia. Oxford: Butterworth-Heinemann, 2004.
4. Tanner PH. Patophysiological changes in the elderly. Best Pract Res Clin Anaesthesiol 2003; 17:163-77.
5. Muravcik S. Preoperative assessment of the elderly. Anesthesiol Clin North Amer 2000; 18: 71-89.
6. Urban MK. Anesthesia for orthopedic surgery. In: Miller RD, Ed. Miller's Anesthesia. 7th Ed. Philadelphia: Churchill Livingstone, 2009: 2241-69.
7. Fleischer LA, Beckmann JA, Brown KA , Calkins H, Chaikoff EI, Fleischmann KE, Freeman WK, Froeblich JB, Kasper EK, Kersten JR, Riegel B. ACC/AHA 2000 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. Circulation 2007; 116: 1971-96.
8. McDonald SB. Is neuraxial blockade contraindicated in the patient with aortic stenosis? Reg Anesth Pain Med 2004; 29:496-502.
9. Callaghan LC, Edward ND. Utilisation of the preoperative ECG. Anaesthesia 1995; 50: 488-90.

10. Perez A, Planell J, Bacardaz C, Honwif A, Franci J, Broton C, Congost L, Bolibar I. Value of routine preoperative tests. Br J Anaesth 1995; 74:250-6.
11. Provenzano G. Chronic pulmonary toxicity of methotrexate and rheumatoid arthritis. Rheumatology 2003; 42:802-3.
12. Lisowska B. Rutkowska-Sak L. Maldyk P. Anaesthesiological problems in patients with rheumatoid arthritis undergoing orthopaedic surgeries. Clin Rheumatol 2008; 27:553-6.
13. Leung CC, Yu KS. Management of difficult spinal anesthesia. Anaesth Intensiv Care 2002; 30:105.
14. Whinney C. Perioperative medication management: general principles and practice applications. Cleve Clin J Med 2009; 76 (Suppl 4):S126-32.
15. Rosencher N., Bellamy L., Arnaout L. Total hip and knee arthroplasty: an anaesthetist's perspective. J Bone Joint Surg Br 2008; 90:S13-17.
16. Crowley M, Fischer B. Routine anaesthesia for joint replacement surgery. Anesth and Int Care Med 2008; 7: 377-80.
17. Gonano C, Leitgeb U, Sitzwol C: Spinal versus general anesthesia for orthopedic surgery. Anesth Analg 2006; 102:524-9.
18. Tripković B. Osobitosti anestezije pri ortopedskim zahvatima. U Klinička anesteziologija Jukić M. i sur. 736-746. Medicinska naklada Zagreb, 2005.
19. Kakar PN. Anesthesia for joint replacement surgery: issues with coexisting diseases. J Anaesthesiol Clin Pharm 2011; 27:315-322.
20. Šmigovec E, Sakić K, Tripkovć B. The laryngeal mask – news in orthopedic anesthesia. Liječ Vjesn 1993; 115:166-9.
21. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, Sage D, Futter M, Saville G, Clark T, MacMahon S. Reduction of postoperative mortality and morbidity with epidural and spinal anesthesia: Results from overview of randomized trials. BMJ 2000; 321:1-12.
22. Macfarlane AJ, Prasad GA, Chan WS. Does regional anesthesia improve outcome after total hip arthroplasty? A systemic review. Br J Anaesth 2009; 103: 335-45.
23. Engesaetetr LB. Antibiotis prophylaxis in total hip arthroplasty. Acta Orthop Scand 2003; 74:644-56.
24. Meehan J, Sahali AA, Nguyen H. Prophylactic antibiotics in hip and knee arthroplasty. J Bone Joint Surg Am 2009; 91:2480-9.
25. Ahmad R, Than J, Nagvi G. Supports used for positioning in hip arthroplasty. Am R Coll Surg Engl 2010; 18:180-5.
26. Winkler M. Aggressive warming reduces blood los during hip arthroplasty. Anesth Analg 2000; 91:978-84.
27. Bierbaum BE, Callaghan JJ. Galante Jo. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg Am 1999; 81: 2-10.
28. Munoz M, Garcia-Erce A: Blood conservation strategies in major orthopaedic surgery: efficacy, safety and European regulations. Vox Sanguinis 2009; 96:1-13.
29. Enderby GEH, Eckenhoff JE: Hypotensive anesthesia, Churchill Livingstone, London 1985.
30. Rajesparan K. The effect of intravenous bolus of tranaxemic acid on blood loss in total hip replacement J Bone Joint Surg Br 2009; 91:778-89.
31. Eubanks JD. Antifibrinolytics in major orthopaedic surgery. J Am Acad Orthop Surg 2010; 18:132-8.
32. Šakić K,. Tripković B.: Autotransfuzija, tromboprofilaksa i perioperacijsko krvarenje. Knjiga tečaja. Zagreb: Medicinska naklada, 2008.
33. Hailer NP. Uncemented and cemented total hip arthroplasty in the Swedish hip arthroplasty register. Acta Orthop 2010; 81:34-41.
34. Donaldson AJ, Thomson HE, Harped NJ. Bone cement implantation syndrome. Br J Anaesth 2009; 102:12-22.
35. Lafont ND, Kalonji MK, Barre J et al. Clinical features and echocardiography of embolism during cemented hip arthroplasty. Can J Anesth 1997; 44:112-7.
36. Ereth MH. Weber JG, Abbel JW. Cemented versus noncemented total hip arthroplasty-embolism, haemodynamics and intrapulmonary shunting. Mayo Clinic Proc 1992; 67:1066-74.
37. Murphy P, Byrick R, Edelist G. Transesophageal echocardiographic changes associated with cemented arthroplasty. Anesthesiology 1994; 81:A753.
38. Parvizi J. Sudden death during primary hip arthorplasty. Clin Orthop Relat Res 1999; 369:39-48.
39. Byrick RJ. Cement implantation syndrome: a time limited embolic phenomenon. Can J Anaesth 1997; 44:107-11.
40. Sherman RP. The role of lavage in preventing haemodynamic and blood gas changes during cemented arthroplaty. J Bone Joint Surg Am 1983; 65:500-6.
41. Francis CH, Pellegrini V, Totterman S.Prevention of deep vein thrombosis after total hip arthroplasty. J Bone Joint Surg Am 1997; 79:1365-1372.
42. Geerts HW, Heit J, Clagett GP, Pineo GF, Colwell CW, Anderson . Prevention of venous thromboembolism, Chest 2001; 119:S132-175.
43. Liu S, Carpenter RL, Neal. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology 1995; 82:1474-1506.
44. Breivik H, bang U. Nordic guidelines for neuraxial blocks in disturbed hemostasis from the Scandinavian Society of Anesthesiology and Intensive Care Medicine. Acta Anesthesiol Scand 2010; 54:16-41.
45. Geerts WH, Heit JA, Clagett GP et al. Prevention of venous thromboembolism. Chest 1987; 119:S132-175.
46. Hull RD. Extended out-of-hospital low molecular weight heparins prophylaxis against deep venous thrombosis in patients after hip arthroplasty. Ann Intern Med 2001; 135:858-869.
47. Geerts WH, Berquist D, Pineo GF et al. Prevention of venous thromboembolism: American College of Chest Physicians Guidelines (8th edition), Chest 2008; 133:S381-453.
48. Weitz JI, Hirsh J, Sammama MM. New antithrombotic drugs. Chest 2008; 133:S234-256.
49. Vandermeulen EP, Van Akeen H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. Anasth Analg 1994; 79:1165-1177.
50. Horlocker T, Wedel D, Benzon H et al. Regional anesthesia in the anticoagulated patient: Definig the risks (The Second ASRA consensus conference on neuraxial anessthesia and anticoagulant). Reg Anesth Pain Med 2003; 28:172-97.
51. Wysowski D. Spinal and epidural hematoma and low molecular weight heparin. N Engl J Med 1998; 38:1774-1775.

52. Holocker TT, Heit IA. Low molecular weight heparin: biochemistry, pharmacology, perioperative prophylaxis regimens, and guidelines for regional anesthesia management. Anesth Analg 1997; 85:874-85.
53. Horlocker TT, Wedel DJ. Neuroaxial blockade and low molecular weight heparin. Reg Anesth 1998; 23:164-77.
54. Horlocker TT. Low molecular weight heparin and neuroaxial anesthesia. Thrombosis Res 2001; 101:141-154.
55. Vadivelu N. Recent advances in postoperative pain management. Yale J Biol Med 2010; 83:11-25.
56. Singelyn SJ. Postoperative analgesia after total hip arthroplasty: i.v. PCA with morphine, patient controlled epidural analgesia, or continuous "3-in-1" block? J Clin Anesth 1999; 11:550-9.
57. Biboulet P. Morau D. Aubas P. Postoperative analgesia after total hip arthroplasty: comparison of intravenous patient cotrolled analgesia with morphine and single injection of femoral or psoas compartment block. Reg Anesth Pain Med 2004; 29:102-9.
58. Ettrich U, Seifert J, Scharnagel R. A multimodal and multidisciplinary postoperative pain management concept. Orthopade 2007; 36:544-51.
59. Gwirtz H. The safety and efficacy of intrathecal opioid analgesia for acute postoperative pain. Anest Analg 1999; 88:599-604.
60. Rathmell JP, Lair TR, Nauman B. The role of intrathecal drugs in the treatment of acute pain. Anesth Analg 2005; 101:S30-S40.
61. Souter AJ, Fredman B, White PF. Controversies in the perioperative use of nonsteroid anti-inflammatory drugs. Anesth Analg 1994; 79:1178-80.
62. Grass P. Patient controlled analgesia. Anesth Analg 2005; 101:S44-61.
63. Sinatra RS, Jahr JS, Reynolds LW. Efficacy and safety of single and repeated administration of 1 gram intravenous Acetaminophen injection (Paracetamol) for pain management after major orthopedic surgery. 2005; 102:822-31.
64. Liu SS, Salinas FV. Continous plexuas and peripheral nerve blocks for postoperative analgesia. Anesth Analg 2003; 96:63-72.
65. Garlit S, Reinhardt S, Mollman A. Continuous spinal analgesia or opioid-added continuous epidural analgesia for postoperative pain control after hip replacement. EJA, 2004; 21:708-14.
66. Gandhi K, Viscusi E. Multimodal pain management techniques in hip and knee arthroplasty. NYSORA, 2009; 13:1-10.
67. Maheshwari A, Blum J, Shekhar L. Multimodal pain management after total hip and knee arthroplasty. Clin Orthop Relat Res 2009; 467:1418-1423.
68. Parvatneni HK, Shah VP, Howart H et all. The use of local periarticular injections in the management of postoperative pain after total hip and knee replacement: a multimodal approach. Instr Course Lect. 2007; 56:125-131.
69. Rasmussen ML, Mathiesen O. Dierking G, Christensen BV, Hilsted KL, Larsen TK, Dahl JB. Multimodal analgesia with gabapentin, ketamine and dexamethasone in combination with paracetamol and ketorolac after hip arthroplasty: a preliminary study. EJA 2010; 27:324-30.

Anestezija kod ugradnje totalne endoproteze kuka

Branko Tripković
Klinika za ortopediju, KBC Zagreb, Hrvatska

SAŽETAK

Ugradnja umjetnog zgloba kuka je česta i uspješna metoda liječenja kod poremećaja kuka praćenih boli i gubitkom normalne funkcije. Broj ovih operacija u stalnom je porastu, te se velika pažnja posvećuje poboljšanju perioperacijskog liječenja ovih bolesnika. Razdoblje od 2001. do 2010. godine proglašeno je za *Desetljeće kostiju i zglobova*, te su mnoge inovacije, kao što je minimalno invazivna kirurška tehnika, uvedene u kliničku praksu. Također, došlo je do znatnog napretka u anesteziološkom liječenju ovih bolesnika, s tim da još uvijek nema definitivnog stava o optimalnom tipu anestezije i analgezije. Sam operacijski zahvat karakteriziraju značajni perioperacijski poremećaji kao što su kardiovaskularne promjene, velika učestalost tromboembolijskih komplikacija, moguće značajno perioperacijsko krvarenje, mogući poremećaji uzrokovani koštanim cementom, a izrazito je visok nivo postoperacijske boli. Anesteziološka skrb ovih bolesnika uključuje prijeoperacijsku pripremu, te intraoperacijsko i postoperacijsko liječenje. Za uspješan ishod liječenja značajna je prijeoperacijska priprema i planiranje da bi se postiglo optimalno stanje prije operacijskog zahvata i da bi se omogućilo najbolje anesteziološko liječenje.

U ovom članku razmatraju se svi problemi prijeoperacijske pripreme. Prikazani su najnoviji podaci o prednostima regionalne anestezije. Razmatraju se mogući intraoperacijski poremećaji, kao i načini njihovog sprječavanja. Posebno su prikazani problemi liječenja postoperacijske boli, te značaj tromboprofilakse, gdje se prikazuju i recentne preporuke koje uključuju i nove antikoagulantne lijekove. Konačan rezultat napretka u anesteziji zadnjih desetljeća jeste značajno smanjenje perioperacijskog morbiditeta i mortaliteta kod ovih bolesnika. Za uspješnu anesteziološku skrb ovih bolesnika preporučuje se uvijek dobro pripremiti bolesnika za operacijski zahvat, analizirati prijeoperacijski status, odabrati optimalnu anesteziološku tehniku, te provoditi tromboprofilaksu i postoperacijsku analgeziju prema prihvaćenim preporukama.

Ključne riječi: anestezija, endoproteza kuka, regionalna anestezija, tromboprofilaksa, terapija boli.

REVIEW

Diagnosis and treatment of peri-prosthetic infections in total hip replacement

Damir Hudetz[1,2], Eduard Rod[1], Andrej Radić[1], Alan Ivković[1,2]

[1]Orthopaedic Surgeon, St. Catherine Specialty Hospital, Zabok [2]Department for Orthopaedic Surgery, University Hospital "Sveti duh", Zagreb; Croatia

ABSTRACT

Total hip replacement (THR) has a very good clinical outcome. Peri-prosthetic infection is a severe complication with infection rates 0.5-2% after primary THR. Systematic reviews and meta-analyses published in recent years have allowed drafting of evidence based guidelines for diagnosis and treatment of peri-prosthetic infection after THR. If an implant related infection is suspected, a complex standardised procedure should be carried out. The most commonly cultured microorganisms causing peri-prosthetic infections are coagulase-negative staphylococci and *S.aureus* followed by mixed flora, streptococci, gram-negative bacilli, enterococci and anaerobes. Different treatment strategies can be applied regarding virulence of a specific pathogen, mechanical stability of the implant and patient's condition. Treatment options always include antibiotic therapy with/without surgical procedures like debridement, one/two stage approach or resection arthroplasty.

Key words: total hip replacement, peri-prosthetic infection, diagnostic, antibiotic treatment

Corresponding author:
Damir Hudetz
Orthopaedic Surgeon,
St. Catherine Specialty Hospital
Bračak 8, 49210 Zabok, Croatia
Phone: +385 49 204 867;
fax.: +385 49 204 886;
E-mail: ortohud@gmail.com

Original submission:
02 November 2011;
Accepted:
16 November 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):152-159

INTRODUCTION

We have reviewed recent advances in the prevention, diagnosis and treatment of infections associated with hip joint endoprostheses. Total hip replacement (THR) is a highly efficacious and cost effective procedure for moderate to severe osteoarthritis. With the aging of population the annual number of performed surgical procedures for hip replacement rises. Bearing in mind relatively low rates of complications like aseptic loosening, infection, dislocation, fracture, technical error, implant fracture, polyethylene wear or pain through time after primary surgery, THR is a very often advocated treatment option by orthopaedic surgeons. The incidence of infection following hip replacement surgery is low and ranges from 0.5% to 2% (1-3), however with onset of such a complication patients suffer from devastating conditions such as prolonged hospitalization, poor functional outcome, sepsis and additional surgical procedures. Rates of infection following hip replacement differ respectively to deep or superficial presentation of infection, primary or revision procedure and total replacement or hemiarthroplasty. Furthermore, the incidence of infection depends on the type of surgical procedure, soft-tissue status, general patient condition and prophylactic administration of antibiotics. In cases of primary total hip replacement the incidence of infection is reported to be of 0.7%, 1.26%, 1.4%, respectively by Norwegian Arthroplasty Register, English mandatory surveillance system and Canadian experience in 1993 consecutive total hip arthroplasties performed by a single surgeon (1,2,4). Most infections after THR are treated with additional surgery. Reoperation has to be distinguished from revision. Reoperation refers to any new hip operation on a patient who has previously undergone hip replacement (e.g. reoperation for superficial infection). Revision refers to exchange or removal of one or both components of endoprosthesis.

Implant related infections differ from other infections in humans in terms of pathogenesis (5). This type of infection results from colonization of the artificial surface by microorganisms that are able to form biofilm (6). Gristina (7) described the process of initial implant colonization as a race for the surface between host cells, extracellular matrix proteins and bacteria (Figure 1). Microorganisms forming biofilms live clustered together in a highly hydrated extracellular matrix attached to surface (8). Depletion of metabolic substances and accumulation of waste products in biofilms causes microbes to enter into a stationary state, rendering them up to 1000 times more resistant to antimicrobial agents than their free-living planktonic counterparts (9, 10). Implant related infections generally occur exogenously during insertion of the implant (intraoperatively), during disturbed wound healing (postoperatively) or less frequently by hematogenous dissemination in late phase after surgery (8). The most common microorganisms causing implant related infection in hip replacement surgery are *S. aureus,* coagulase-negative staphylococci, Gram negative aerobic rod-shaped bacteria and streptococci (3).

PREVENTION OF PERI-PROSTHETIC INFECTION

In order to prevent hip implant related infection the most effective strategy is to apply all means of antisepsis and asepsis. Risk factors for implant related infection are divided between patient, surgery itself and environment. Patients with poor nutritional status, diabetes, BMI>40, coexistent remote infections (urinary tract, dental), prolonged preoperative hospitalization and those who smoke have increased risk for postoperative infection (11). Among patient risk factors nasal carriage of *S. aureus* has been clinically recognized and some authors advocate preoperative nasal screening and mupirocin treatment (12, 13). Among many operation risk factors proper skin antisepsis is extremely important and feasible with the use of effective antiseptics like chlorhexidine, octenidine, io-

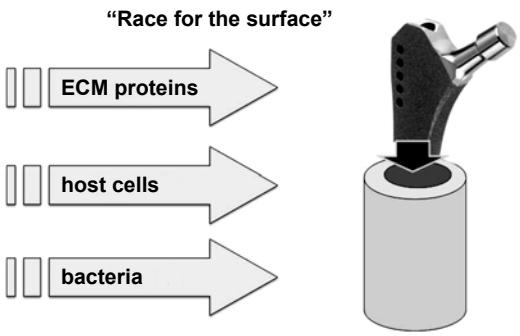


Figure 1. "Race for the surface" of endoprosthesis during implantation (7)

dine or polyhexanide. Preoperative shaving is associated with a higher risk for implant related infection but immediate shaving before surgery is better. Drains should be passed through a separate incision away from the wound and removed as soon as possible (24 hours), with the use of closed suction systems (14). Operating room air has to have positive pressure with 20 air changes per hour provided, microbial count in OR has to be proportional to the number of people and their movement must be controlled (15). Sterilization of instruments is an essential part of aseptic technique and has to be performed with validated methods. There was found no evidence in several trials that plastic adhesive antimicrobial drapes reduce surgical site infection rate (16).

Antimicrobial prophylaxis and its role in preventing peri-prosthetic infection is controversial. A systemic trial review of antibiotic prophylaxis in total joint replacement surgery has assessed 150 studies (17). The review evaluated and summarized data from 25 randomized controlled trials. The overall peri-prosthetic infection rate with antibiotic prophylaxis was 1% in THR. Surgical antibiotic prophylaxis reduced the incidence of infection in comparison to placebo or no intervention. Single dose prophylaxis was not inferior to multiple dose applications. When cefuroxsime is used as a prophylactic antibiotic, administration 59 to 30 minutes before skin incision is more effective than administration during the last half hour (18).

IMPLANTS AND SURGICAL PROCEDURES IN RELATION TO INFECTION

The presence of implant causes relatively low bacterial inoculum to be sufficient in triggering an infection (19). New trends in orthopaedic surgery pursue less invasive surgical approaches what essentially spares muscles but simultaneously shortens the length of skin incision. The shortened incisions provide more contact of the instruments and implants with the skin surface during surgical procedure what can potentially influence the colonization of implants. Type of material used for the implant, and the ability of bacteria to form biofilm have a weak effect on infection (20). Decisive trigger for infection is the colonization of implants during surgery. Surgical technique influences the amount of avital bone and soft tissue concurrently influencing the size of bacterial inoculum needed to start the infection. New designs of implants with porous structure that enable better bone ingrowth provide larger surface for the bacteria to adhere.

DIAGNOSIS OF PERI-PROSTHETIC HIP INFECTION

There is no single routinely used test to diagnose the infection sufficiently accurately. Therefore, a combination of clinical, laboratory, imaging and microbiology assessment is needed. Clinicians and microbiologists form a team that coordinates a complex diagnostic procedure if a peri-prosthetic infection is suspected. The efficacy of this process has direct impact on the therapy and the outcome of the treatment (3).

Laboratory studies

Peri-prosthetic joint infection can be classified according to the route of infection and time of symptom onset after implantation (Table 1) (21). Clinical findings of a peri-prosthetic infection are characterized by novel or persisting local pain, local reddening, swelling and hyperthermia, persisting secretion, tensioned soft tissue, pyrexia, leukocytosis and a novel or persisting elevation of the C-reactive protein or erythrocyte sedimentation rate (ESR) (22).

Table 1 Classification of peri-prosthetic joint infections (21)

Classification	Characteristic
According to the route of infection	
Perioperative	Inoculation of microorganisms into the surgical wound during surgery or immediately thereafter
Hematogenous	Through blood or lymph spread from a distant focus of infection
Contiguous	Contiguous spread from an adjacent focus of infection (e.g. penetrating trauma, pre-existing osteomyelitis, skin and soft tissue lesions
According to the onset of symptoms after implantation	
Early infection (< 3months)	Predominantly acquired during implant surgery or the following 2 to 4 days ad caused by highly virulent organisms (e.g. S.aureus or gram-negative bacilli)
Delayed or low-grade infection (3-24 months)	Predominantly acquired during implant surgery and caused by less virulent organisms (e.g. coagulase negative staphylococci or P. acnes)
Late infection (> 24 months)	Predominantly caused by hematogenous seeding from remote infections

Blood leukocyte count and differential are not sufficiently discriminative to predict the presence or absence of infection (23). After the surgery CRP is elevated and returns to normal values within weeks. In the postoperative phase dynamic data with repeated measurements of CRP are more valuable than a single CRP value. A secondary increase of CRP in postoperative phase after early decline is highly presumptive for infection. Serum procalcitonin is a helpful diagnostic marker supporting clinical and microbiological findings for more reliable differentiation of infectious from noninfectious causes of fever after orthopaedic surgery (24).

Imaging studies

Imaging plays a minor role in early infection whereas it is useful in detection of late and delayed peri-prosthetic infections. It is possible to assess the extent of infection by the means of imaging diagnostic tools. Plain X-rays can be useful after the implantation of a endoprosthesis but are neither sensitive nor specific for infection (25). Radiolucency around the implant may indicate either instability or infection. A rapid development of a continuous radiolucent line greater than 2 mm or severe focal osteolysis within the first year is often associated with infection. Arthrography with the use of a contrast may present synovial recesses and abscesses as typical signs of infection (26). By means of ultrasonography fluid effusions around the prosthesis can be visualized and potentially aspirated. Bone scintigraphy with ^{99m}Tc has excellent sensitivity but a low specificity for assessing peri-prosthetic joint infection (27). During the first postoperative year increased bone remodelling around the prosthesis is present and infection can be hardly distinguished from aseptic loosening. A lack of ^{99m}Tc accumulation around the hip can demonstrate the lack of vascularisation and dead bone. Scintigraphy with ^{99m}Tc-labelled monoclonal antibodies has a higher accuracy for detection of infection. Computed tomography (CT) can provide more detailed information about the extent of bone necrosis, whereas magnetic resonance imaging (MRI) displays an improved resolution for soft tissue abnormalities. Positron emission tomography (PET) and PET-CT appear to be valuable new tools in diagnosis of metallic implant related infections (28).

Histopathology and microbiological studies

Histopathology of the tissue around the prosthesis can demonstrate acute inflammation with sensitivity >80% and specificity>90% (29). Inflammatory cells count and the degree of infiltration may vary considerably between specimens from the same patient and even between those from different regions of the implant. Therefore, areas with the most intensive inflammatory changes should be assessed and an average count should be obtained from at least ten power fields (30). Acute inflammation is defined as from >1 to >10 neutrophils per high power field. Histopathology cannot identify the cause of infection and can be difficult in patients with pre-existing inflammatory joint disorders.

Preoperative aspiration of peri-prosthetic fluid and intraoperative tissue cultures provide the most accurate specimens for detecting the infecting microorganism. Culture of aspirated superficial wound or sinus tract represents microbial colonization from the surrounding skin and can therefore be misleading. Culture of aspirated synovial fluid detects the infecting microorganisms in 45-100% (29) and could be improved by inoculation into a paediatric blood culture bottle (31).

At least three intraoperative tissue areas should be sampled and paired for microbiology and histopathology (32). Swabs of the infected tissue should be avoided due to very low sensitivity. If possible, any antimicrobial therapy should be avoided and discontinued 14 days before tissue sampling for culture (33), in cases of revision surgery antibiotic prophylaxis should not be started before all the specimens have been collected (34). Peri-prosthetic tissue cultures provide the most accurate specimens for the detection of the causative microorganism ranging from 65-94% (32,33,35).

The removed parts of endoprostheses can be cultured in enriched broth media enabling direct sampling of the infection site. Sonication of the implants in order to dislodge adhered bacteria increases the sensitivity of the culture (36).

TREATMENT OF IMPLANT RELATED INFECTIONS FOLLOWING THR

The goal of treatment of a peri-prosthetic hip infection is to restore joint function and to alleviate pain. It can be achieved only by eradicating the infection. The treatment itself is not a uniform straightforward procedure like in cases of primary total hip replacements. There are many obstacles on the way to reach this goal, among which is the fact that the implants have no perfusion and antibiotics can reach them via diffusion. Furthermore insufficient local antibiotic concentrations can occur in avital bone tissue despite adequate systemic antibiotic concentrations (37). According to the isolated pathogen, an individually adapted antibiotic and surgical treatment should be carried out.

Antibiotic therapy

Standard antimicrobial-susceptibility test cannot be used in implant related infections to reliably predict the outcome (38, 39). Characteristic of an antimicrobial agent dealing with peri-prosthetic hip infection should be bactericidal activity against surface adhering, biofilm forming, slow growing microorganisms (6,39,40). Rifampin fulfils these requirements and has shown antimicrobial activity against staphylococci in *in vitro*, animal and clinical studies (39, 41-43). Staphylococci develop resistance to rifampin therefore it should never be administered alone (44). Quinolones, ciprofloxacin and ofloxacin can be combined with rifampin in patients with bone or joint infection (42). Due to increasing resistance of staphylococci to quinolones alternative antimicrobial synergies with rifampin are needed. Potential adjuvant antimicrobial agents are fusidic acid, timethoprim-sulfamethoxazole, minocyline and linezolid. The microorganism should be susceptible to oral antimicrobial agents with good bioavailability since long term therapy is needed, otherwise use of an intravenous access device for outpatient treatment is needed (45,46).

Surgical therapy

Surgical treatment includes debridement with retention of the prosthesis, one- or two-stage exchange, resection arthroplasty, arthrodesis or exarticulation (47).

Debridement involving removal of the hematoma, fibrous membranes, sinus tracts and devitalized tissues should only be preformed if time from implantation to peri-prosthetic infection is less than three weeks. The implant in this treatment option should not exhibit mechanical instability, soft tissue should be in good condition and causing microorganism should be susceptible to antimicrobial therapy. The debridement is followed with a prolonged antibiotic treatment of up to six months (45).

One-stage exchange includes removal of all implants, meticulous debridement, lavage and reimplantation of a new endoprostheis within the same procedure. In case of a cemented THR the identification of the pathogen prior to revision is needed in order to prepare custom made bone-cement loaded with specific antibiotic. If the pathogen is isolated and the patient has no signs of severe systemic infection it is recommended to start the antimicrobial treatment two to three weeks prior to revision (45). The revision surgery is followed by an intravenous antibiotic treatment and long-term oral therapy (48).

Two-stage revision surgery includes removal of all implants and bone cement, accompanied by debridement and lavage. Custom-made antibiotic-loaded bone spacer can be implanted at the end of first stage. The cement spacer is left to keep the limb in correct alignment and allows partial mobility. Drainage with irrigation and suction is preferable to drainage alone (49). The surgical procedure is followed by two weeks of intravenous antibiotic therapy, followed by four weeks of oral antibiotic administration. Prior to reimplantation aspiration of tissue could be performed. If there are no signs of infection revision surgery is indicated. Second surgical procedure involves again thorough debridement and than reimplantation. Post-operative antibiotic prophylaxis is carried for another four to six weeks (48).

Girdlestone resection arthroplasty consists of permanent surgical removal of all implants and debridement without reimplantation. Beside this procedure there are treatment options like arthrodesis and disarticulation as salvage procedures.

In conclusion, many improvements have been made in understanding of the implant related infection pathogenesis in recent decades. Better

understanding of microbial interaction with the implant and mechanisms of resistance has led to a more rational approach in antimicrobial therapy. Advances in the diagnosis and treatment algorithms have sequentially evolved. Peri-prosthetic infection after total hip replacement remains a challenging complication. If an implant-associated infection is suspected, a complex diagnostic process is undertaken. Once peri-prosthetic infection is assessed, different treatment strategies can be deployed regarding time of infection onset, patient condition and microbial agent susceptibility. Antibiotic therapy without surgical procedure cannot heal a peri-prosthetic infection but can suppress septic condition in inoperable patients. Usually various surgical procedures are combined along with antibiotic therapy. Prevention of the peri-prosthetic infection in THR remains best possible treatment. This goal can be achieved with the use of antibiotic prophylaxis and with aseptic conditions at the time of surgery.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Hamilton H, Jamieson J. Deep infection in total hip arthroplasty. Can J Surg 2008; 51:111-7.
2. Wilson J, Charlett A, Leong G, McDougall C, Duckworth G. Rates of surgical site infection after hip replacement as a hospital performance indicator: analysis of data from the English mandatory surveillance system. Infect Control Hosp Epidemiol 2008; 29:19-26.
3. Geipel U, Herrmann M. The infected implant. Part 1: bacteriology. Orthopade 2004; 33:1411-26; 1427-8.
4. Engesaeter LB, Dale H, Schrama JC, Hallan G, Lie SA. Surgical procedures in the treatment of 784 infected THAs reported to the Norwegian Arthroplasty Register. Acta Orthop 2011; 82:530-7.
5. Frommelt L. Principles of systemic antimicrobial therapy in foreign material associated infection in bone tissue, with special focus on periprosthetic infection. Injury 2006; 37 (Suppl 2):S87-94.
6. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science 1999; 284:1318-22.
7. Gristina AG, Naylor P, Myrvik Q. Infections from biomaterials and implants: a race for the surface. Med Prog Technol 1988; 14:205-24.
8. Trampuz A, Zimmerli W. Diagnosis and treatment of infections associated with fracture-fixation devices. Injury 2006; 37 (Suppl 2):S59-66.
9. Donlan RM. Biofilms: microbial life on surfaces. Emerg Infect Dis 2002; 8:881-90.
10. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet 2001; 358:135-8.
11. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999; 20:250-78.
12. Bajolet O, Toussaint E, Diallo S, Vernet-Garnier V, Dehoux E. Is it possible to detect Staphylococcus aureus colonization or bacteriuria before orthopedic surgery hospitalization?. Pathol Biol 2010; 58:127-30.
13. (13) Lederer SR, Riedelsdorf G, Schiffl H. Nasal carriage of meticillin resistant Staphylococcus aureus: the prevalence, patients at risk and the effect of elimination on outcomes among outclinic haemodialysis patients. Eur J Med Res 2007; 12:284-8.
14. Gaines RJ, Dunbar RP. The use of surgical drains in orthopedics. Orthopedics 2008; 31:702-5.
15. Friedman C, Newsom W, eds. Prevention of Surgical Site Infections. Basic Concepts of Infection Control. International Federation of Infection Control IFIC, Northen Ireland, 2008
16. Webster J, Alghamdi AA. Use of plastic adhesive drapes during surgery for preventing surgical site infection. Cochrane Database Syst Rev 2007:CD006353.
17. Glenny A, Song F. Antimicrobial prophylaxis in total hip replacement: a systematic review. Health Technol Assess 1999; 3:1-57.
18. Weber WP, Marti WR, Zwahlen M, Misteli H, Rosenthal R, Reck S, et al. The timing of surgical antimicrobial prophylaxis. Ann Surg 2008; 247:918-26.
19. Darouiche RO. Device-associated infections: a macroproblem that starts with microadherence. Clin Infect Dis 2001; 33:1567-72.
20. Hudetz D, Ursic Hudetz S, Harris LG, Luginbuhl R, Friederich NF, Landmann R. Weak effect of metal type and ica genes on staphylococcal infection of titanium and stainless steel implants. Clin Microbiol Infect 2008; 14:1135-45.
21. Trampuz A, Zimmerli W. Prosthetic joint infections: update in diagnosis and treatment. Swiss Med Wkly 2005; 135:243-51.
22. Ruchholtz S, Tager G, Nast-Kolb D. [The infected hip prosthesis]. Unfallchirurg 2004; 107:307-17.
23. Steckelberg JM, Osmon DR. Prosthetic joint infections. In: Waldvogel FA, Bisno AL, eds. *Infections associated with indwelling medical devices*. 3rd ed. Washington, D.C.: American Society for Microbioloy 2000:173-209.
24. Hunziker S, Hugle T, Schuchardt K, Groeschl I, Schuetz P, Mueller B, et al. The value of serum procalcitonin level for differentiation of infectious from noninfectious causes of fever after orthopaedic surgery. J Bone Joint Surg Am 2010; 92:138-48.

25. Tigges S, Stiles RG, Roberson JR. Appearance of septic hip prostheses on plain radiographs. AJR Am J Roentgenol 1994; 163:377-80.
26. Zimmerli W, Ochsner PE. Management of infection associated with prosthetic joints. Infection 2003; 31:99-108.
27. Corstens FH, van der Meer JW. Nuclear medicine's role in infection and inflammation. Lancet 1999; 354: 765-70.
28. Schiesser M, Stumpe KD, Trentz O, Kossmann T, Von Schulthess GK. Detection of metallic implant-associated infections with FDG PET in patients with trauma: correlation with microbiologic results. Radiology 2003; 226:391-8.
29. Trampuz A, Steckelberg JM, Osmon DR, Cockerill FR, Hanssen AD. Advances in the laboratory diagnosis of prosthetic joint infection. Rev Med Microbiol 2003; 14:1-14.
30. Athanasou NA, Pandey R, de Steiger R, Crook D, Smith PM. Diagnosis of infection by frozen section during revision arthroplasty. J Bone Joint Surg Br 1995; 77:28-33.
31. Hughes JG, Vetter EA, Patel R, Schleck CD, Harmsen S, Turgeant LT, Cockerill FR 3rd. Culture with BACTEC Peds Plus/F bottle compared with conventional methods for detection of bacteria in synovial fluid. J Clin Microbiol 2001; 39:4468-71.
32. Atkins BL, Athanasou N, Deeks JJ, Crook DW, Simpson H, Peto TE, McLardy-Smith P, Berendt AR. Prospective evaluation of criteria for microbiological diagnosis of prosthetic-joint infection at revision arthroplasty. The OSIRIS Collaborative Study Group. J Clin Microbiol 1998; 36:2932-9.
33. Spangehl MJ, Masri BA, O'Connell JX, Duncan CP. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. J Bone Joint Surg Am 1999; 81:672-83.
34. Widmer AF. New developments in diagnosis and treatment of infection in orthopedic implants. Clin Infect Dis 2001; 33:S94-106.
35. Pandey R, Berendt AR, Athanasou NA. Histological and microbiological findings in non-infected and infected revision arthroplasty tissues. The OSIRIS Collaborative Study Group. Oxford Skeletal Infection Research and Intervention Service. Arch Orthop Trauma Surg 2000; 120:570-4.
36. Tunney MM, Patrick S, Curran MD, Ramage G, Hanna D, Nixon JR, Gorman SP, Davis RI, Anderson N. Detection of prosthetic hip infection at revision arthroplasty by immunofluorescence microscopy and PCR amplification of the bacterial 16S rRNA gene. J Clin Microbiol 1999; 37: 3281-90.
37. Gustilo RB, Merkow RL, Templeman D. The management of open fractures. J Bone Joint Surg Am 1990; 72:299-304.
38. Brandt CM, Sistrunk WW, Duffy MC, Hanssen AD, Steckelberg JM, Ilstrup DM, Osmon DR. Staphylococcus aureus prosthetic joint infection treated with debridement and prosthesis retention. Clin Infect Dis 1997; 24:914-9.
39. Zimmerli W, Frei R, Widmer AF, Rajacic Z. Microbiological tests to predict treatment outcome in experimental device-related infections due to Staphylococcus aureus. J Antimicrob Chemother 1994; 33:959-67.
40. Anderl JN, Zahller J, Roe F, Stewart PS. Role of nutrient limitation and stationary-phase existence in Klebsiella pneumoniae biofilm resistance to ampicillin and ciprofloxacin. Antimicrob Agents Chemother 2003; 47:1251-6.
41. Schwank S, Rajacic Z, Zimmerli W, Blaser J. Impact of bacterial biofilm formation on in vitro and in vivo activities of antibiotics. Antimicrob Agents Chemother 1998; 42:895-8.
42. Widmer AF, Gaechter A, Ochsner PE, Zimmerli W. Antimicrobial treatment of orthopedic implant-related infections with rifampin combinations. Clin Infect Dis 1992; 14:1251-3.
43. Drancourt M, Stein A, Argenson JN, Roiron R, Groulier P, Raoult D. Oral treatment of Staphylococcus spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. J Antimicrob Chemother 1997; 39:235-40.
44. Kadurugamuwa JL, Sin LV, Yu J, Francis KP, Purchio TF, Contag PR. Noninvasive optical imaging method to evaluate postantibiotic effects on biofilm infection in vivo. Antimicrob Agents Chemother 2004; 48:2283-7.
45. Zimmerli W, Trampuz A, Ochsner PE. Prosthetic-joint infections. N Engl J Med 2004 ; 351: 1645-54.
46. Osmon DR, Berbari EF. Outpatient intravenous antimicrobial therapy for the practicing orthopaedic surgeon. Clin Orthop Relat Res 2002:80-6.
47. Westrich GH, Salvati EA, Brause B. Postoperative infection. In: Bono JV, McCarty JC, Thornhill TS, Bierbaum BE, Turner RH, eds. Revision total hip arthroplasty. New York: Springer-Verlag 1999:371-90.
48. Lohmann CH, Furst M, Niggemeyer O, Ruther W. The treatment of periprosthetic infections. Z Rheumatol 2007; 66:28-33.
49. Schafroth M, Zimmerli W, Brunazzi M, Ochsner PE. Infections. In: Ochsner PE, ed. Total hip replacement. Berlin: Springer Verlag 2003:65-90.

Dijagnoza i liječenje periprostetičkih infekcija nakon ugradnje totalnih endoproteza kuka

Damir Hudetz[1,2], Eduard Rod[1], Andrej Radić[1], Alan Ivković[1,2]

[1]Specijalna bolnica za ortopediju, kirurgiju, neurologiju i fizikalnu medicinu i rehabilitaciju ž'Sv. Katarina'', Zabok; [2]Zavod za ortopediju, Klinička bolnica "Sveti duh", Zagreb; Hrvatska

SAŽETAK

Operacija ugradnja totalne endoproteze (TEP) kuka pokazuje vrlo dobre kliničke rezultate. Periprostetička infekcija jedna je od najtežih komplikacija ovog zahvata sa stopom od 0.5% do 2% nakon primarne ugradnje. Sistematski pregledni članci i metaanalize, objavljene zadnjih godina, omogućavaju objavljivanje smjernica na temelju znanstvenih dokaza za dijagnozu i liječenje periprostetičkih infekcija nakon ugradnje TEP kuka. Ako postoji sumnja na infekciju oko ugrađenog implantata potrebno je pokrenuti složeni standardizirani dijagnostički postupak. Mikroorganizmi koji najčešće uzrokuju periprostetičke infekcije su koagulaza-negativni stafilokoki i *S. aureus*, a slijede ih miješana flora, streptokoki, gram-negativni bacili, enterokoki i anaerobi. Različite strategije liječenja mogu se primijeniti ovisno o virulenciji uzročnika, mehaničkoj stabilnosti implantata i stanju pacijenta. Opcije liječenja uvijek uključuju antibiotike s ili bez operacijskog liječenja. Operacijsko liječenje uključuje opcije debridementa, revizije u jednom ili dva koraka, ili resekcijske artroplastike.

Ključne riječi: totalna endoproteza kuka, periprostetička infekcija, dijagnostika, antimikrobno liječenje

ORIGINAL ARTICLE

Minimally invasive hip arthroplasty: advantages and disadvantages

Božidar Šebečić, Mario Starešinić, Vencel Čuljak, Mladen Japjec

Department of Traumatology, Surgery Clinic, Merkur University Hospital, Zagreb, Croatia

ABSTRACT

Aim To present the method and advantages of anterior minimally invasive surgery (AMIS) in coxarthrosis and hip fractures treatment.

Methods During 2008 and 2009, 35 patients were treated with AMIS method. They were compared with 35 patients treated with lateral, transgluteal approach (control group) in the same period. All operations were performed by the same surgical team. The main reason for surgery was hip arthrosis, only two patients in AMIS group underwent surgery because of femoral neck fracture. Early postoperative complications and functional status are followed by Haris Hip Score (HHS).

Results Operation time was shorter and postoperative blood loss was lesser in AMIS group (78 min, 490 ml) than in the control group (85 min, 570 ml). In the AMIS group one patient had each post-operative knee pain, fractured tip of a large trochanter, acetabular overreaming, perforation of shaft with rasp, and two patients had parestesis *n.cutaneus femoris lat*. They had no infections or hip luxation. In the control group early hip luxation and superficial wound infections have occurred in one and two cases, respectively. Patients in the AMIS group were more satisfied, demanded less analgesics and their rehabilitation was faster. Haris Hip Score in the AMIS group after 2 months was 80 compared with 69 in the controls, and after 4 months 92 compared to 88 in controls.

Conclusion AMIS is a safe, reproducible and rewarding technique which provides low morbidity and fast postoperative recovery for the patient.

Key words: minimally invasive, anterior approach, hip, arthroplasty

Corresponding author:
Mladen Japjec
Department of Traumatology, Surgery Clinic, Merkur University Hospital
Zajčeva 19, 1000 Zagreb, Croatia
Phone: +385 1 24 31 390;
fax.: +385 1 24 31 394;
E-mail: japmladen@gmail.com

Original submission:
16 October 2011;
Revised submission:
26 October 2011;
Accepted:
28 October 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):160-165

INTRODUCTION

Total Hip arthroplasty (THA) is one of the most common operations performed in the developed world (1). An increasing older population means that the number of people undergoing this operation is set to rise (1-3). Total hip arthroplasty can reliably reduce pain, improve function, and improve the quality of life in a broad section of patients with end-stage hip arthrosis. In previous years many different operative methods were presented, but in recent years the concept of performing THA through "minimally invasive" techniques was introduced with the potential for decreasing patient pain (4), decreasing operative soft tissue trauma and blood loss, improving patient satisfaction with the procedure and accelerating rehabilitation (5,6).

The mininimal anterior approach for total hip arthroplasty is an old approach first described as the Smith-Petersen (7), modified by Hueter more than 50 years ago. The anterior Hueter approach has been used by Judet for hip joint exposure for arthroplasty techniques since 1947 (8). This approach follows the intermuscular space between the tensor fascia latae and rectus femoris muscles. The lateral femoral circumflex artery and vein should be ligated. This approach provides excellent anterior exposure of the hip joint capsule.

With years of experience of treating hip problems, in the Merkur University Hospital we started with minimal invasive anterior approach hip arthroplasty. The aim of this study was to show the advantages of AMIS in hip arthrosis and fractures treatment compared with standard lateral, transgluteal approach.

PATIENTS AND METHODS

The operation of minimally invasive anterior hip arthroplasty was based on the technique described by Laude (9) and special instruments and prostheses (Medacta, AMIS®) were used for it. In the Department of Traumatology, Surgery Clinic, University Hospital Merkur between January 2008 and December 2009 35 patients were treated with AMIS method, 16 females and 19 males. Average age was 66 years (40-84 years). For most patients (33, 94%) the reason for surgery was hip arthrosis and two patients (6%) were operated because femoral neck fractures (Figure 1). Patients operated with minimally invasive method were compared with 35 patients operated with the lateral transgluteal approach. Control group had 14 female and 21 male with average age of 70 years (45-82 years). Early postoperative complications and functional status were followed by Haris Hip Score (HHS) (10) two and four months after the surgery. Statistical analysis was performed $\chi 2$ test and $p<0.05$ was considered significant.

To enable performance of AMIS with limited surgical visual fields, conventional instruments for the placement of hip prosthesis and operative table must be modified. Operation on ordinary table was possible, but it was much harder, more aggressive towards the skin and muscle, and required the help of more assistants (11,12). The patient was placed in a supine position on a standard orthopedic table equipped with special leg holder which allows traction of the operative extremity, combined with hyperextension, external and internal rotation of the hip, and lowering of foot to the ground during the surgery. The skin incision was started at a point 2 cm below and 1 cm lateral to the antero-superior iliac spine, and was extended 8 cm distally above the fascia of tensor fascia lata muscle (Figure 2). After incising

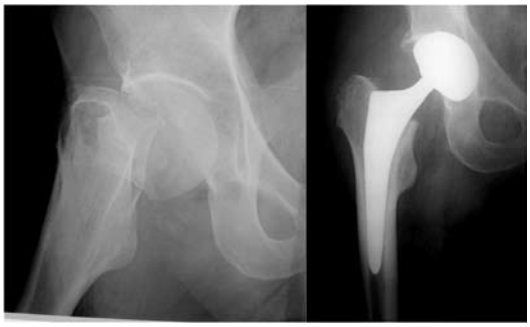


Figure 1. Fractura colli femoris (left) **treated with minimally invasive anterior approach to hip joint (AMIS**) (right) (Šebečić B., 2009)

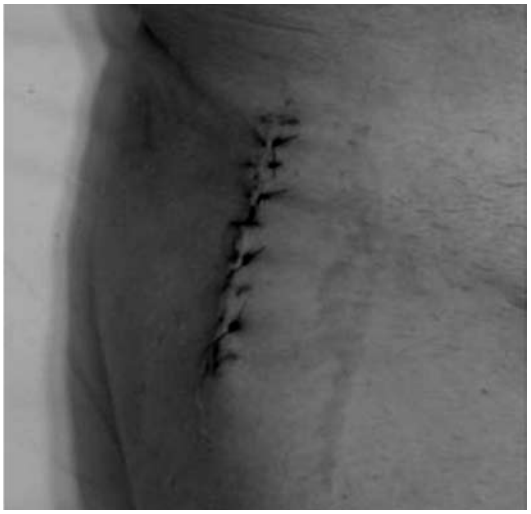


Figure 2. Postoperative wound after anterior minimally invasive surgery (AMIS) in coxarthrosis (Šebečić B., 2009)

the skin and subcutaneous fat, the aponeurosis of the tensor fascia lata muscle was reached. The superficial aponeurosis of the tensor fascia lata was incised, and the tensor fascia lata was displaced laterally and the rectus femoris medially. Anterior circumflex vessel was visualized beneath the innominate aponeurosis and should be ligated. The femoral head and neck are exposed via a partial anterior "V" shape capsuletomy. Joint capsule was spaced with modified Charnley retractor. The neck was osteotomised with an oscillating saw. Following exposure and reaming of the acetabulum, the acetabular component was seated with a curved impactor and oriented in 45°-55° of abduction. The femur was exposed by placing the retractor hook was in the recess of the vastus lateralis ridge. This hook was contoured to avoid soft tissue injury. The leg was then externally rotated to 90°, adducted and locked with the foot on the ground allowing axial access to the proximal femur. The stem was implanted after rasping the femur. The hip was reduced by raising the leg from external rotation to the neutral position and releasing traction. Closure is done after testing of the stability and motion with restoring of the anterior capsule and interrupted Vicryl suture of the tensor fascia. At the end subcutaneous and skin closure was per routine. An aspiration drain was put in and kept in place for two days.

RESULTS

This study was done following both groups of patients during surgery and postoperative recovery period (Table 1). Operation time was shorter, (avg. 78 min, 65-140min) in AMIS group compared to the control group (avg. 85 min, 70-115min). The incision in anterior approach group was 7.5 cm (range 6.5-9 cm) which was significantly shorter than in the lateral approach group, 13 cm (range 11-18cm) ($p<0.01$). Postoperative blood loss was less in AMIS group (avg. 490 mL, 240-1150mL) than in the control group (avg. 570 mL, 350-1280mL). In the control group there was one early hip luxation and two superficial wound infections. The luxation was resolved with closed reposition under general anesthesia. In the AMIS group complications did not include infections or hip luxation but there was one patient with each post-operative knee pain, fractured tip of a large trohanter, acetabular overreaming,

Table 1. Comparison of patients treated by AMIS and classis lateral transgluteal approach hip arthroplasty*

	Operative methods		
	AMIS	**Lateral classic approach**	**Statistical difference between the groups**
Operation time	78 (65-140) min	85 (70-115) min	NS
Incision length	7,5 (6.5-9) cm	13 (11-18) cm	$p<0.01$
Postoperative blood loss	490 (240-1150) ml	570 (350-1280) ml	$p<0.05$
Hospitalization time	10 (7-12) days	12 (9-14) days	NS
Infection	0	2	NS
Postoperative knee pain	1	0	NS
Fracture of great trochanter	1	0	NS
Acetabular overriming	1	0	NS
Hip luxation	0	1	NS
N.cutaneos femoris lesion	2	0	NS
Perforations of the shaft with rasp	1	0	NS
HHS** after 2 months	80.2 pts	69.4 pts	$p<0.01$
HHS after 4 months	92.4 pts	88.1 pts	NS

*AMIS, minimally invasive anterior approach to hip joint; HHS, Haris hip score; NS, non significant

perforation of shaft with rasp, and two patients with transient paresthesies of *n. cutaneus femoris lateralis*. These problems mostly occurred in the initial operations and did not require revision.

Patients in AMIS group were subjectively more satisfied, demanded less analgesics and were discharged from the hospital average two days earlier than control group patients (10 vs. 12). In the AMIS group rehabilitation was faster than in control group. Our protocol for AMIS group included: one month walk with two crutches. The most of our patients in the AMIS group could walk without crutches already eight days after surgery.

Early postoperative complications and functional status were followed by HHS two and four months after surgery. After two months HHS in the AMIS group was 80.2 vs. 69.4 ($p<0.01$) in the control group. After four months HHS was still higher in the AMIS group than in the control group (92.4 vs. 88.1).

DISCUSSION

Over the years many approaches to the hip joint (13-17) have been described. For most of them it is required to cut the muscle to reach the joint, which provides good visualization but also has certain consequences (18-21). The lateral

approach cuts the detachment of the gluteus medius and minimus from the greater trochaner with a higher incidence of postoperative limp (18). The posterior approach preserves the gluteus muscles but needs to cut the posterior hip capsule and the external rotators, which increase the incidence of posterior hip dislocation (19-21). Some studies compared the lateral and posterior approach to the hip and did not indicate a significant difference in the rate of dislocations in both methods, which were 1-5% (22,23). One dislocation that occurred in our control group of 35 patients (2,8%) also showed that these complications were rare, but constant. In contrast, the AMIS group does not require sectioning of muscle, ligaments and tendon to implant the prosthetic components and thus increases stability and reduces the rate of dislocation (12,24,25). In our AMIS group, there was no dislocation, and the low rate of dislocation was also described by Mattta et al. (0.61%) (12) and by Siguier et al. (0.96%) (24).

A smaller skin incision and minimal damage of soft tissue ensure less blood loss, less postoperative pain, a more stable joint and more rapid rehabilitation (4-6). Our patients in the AMIS group compared with the control group had in average 7% shorter operation time (78 vs. 85 min), postoperatively lost 15% less blood (490 vs. 570 ml), headed to rehabilitation earlier and were discharged from hospital two days earlier. Siguer et al (24) reported that most of their patients had quick recovery and were able to walk without crutches practically a few days after the surgery, depending on the age and physical condition. According to our protocol, AMIS group of patients walked with two crutches for one month. Most of them could walk without crutches already 8 days after the surgery, but as a precaution, they were ordered to walk with two crutches for one month. Unlike them, patients in the control group followed our standard protocol under which they walked with two crutches for two months and then with one crutch for another two months.

Despite the small aperture in the body tissues, AMIS usually provides good visualization (4,8,9,12). For safety, the most authors recommend use of fluoroscopy (4-6, 9, 11,12, 24, 26), but as some authors reported (27,28), we also consider that X-ray during surgery is not necessary. To deal with reduced exposure and limited visibility, surgeons should be very familiar with the local anatomy and they need special instruments and traction table device (25). Training and experience are crucial to successfully perform the operation (29,30). Potential complications include intraoperative femoral and ankle fractures (31) and damage of the *n. cutaneus femoris lateralis* (12,26, 32-34). In the AMIS group we had one fractured tip of a large trohanter (3%), acetabular overreaming (3%), perforation of shaft with rasp (3%), and two patients (6%) with transient paresthesies of *n. cutaneus femoris lat*. Aszmann et al (35) identified a few anatomic variants of *n. cutaneus femoris lat*. which showed significant variability in the anatomic location and usually it was very close to the surgical field of the anterior hip approach. Matta et al (12) reviewed 494 hips and observed that some patients had transient *n. cutaneus femoris lat*. injury. While Kennon et al (32,33) had only five (<0.01%) neural lesions on 2132 patients, Rauchbauer (34) reported six injuries (6%) on 100 patients, and Bhargava et al (26) had almost 15% lesions *n .cutaneus femoris lat*. with permanent impairment in 3% of patients. They considered that incision position, subcutaneous dissection plane, retractor placement, tension and soft tissue handling may be factors influencing nerve injury (26). Decreasing operative time and traction on the nerve (26) or adjusting the incision "more lateral"(12) may decrease the incidence. According to Paillard (36*), t*he fracture of femur can be avoided with cautious external rotation of the hip and lowering of the limb, which must be performed without traction. Also, if a femoral fracture occurs, the incision can be extended distally and laterally to expose the femoral shaft (36).

Anterior minimally invasive surgery is not suitable for the treatment of severe hip dysplasia and for revision artroplasty (37). Relative contraindications also include short or varus positioned femoral neck, muscular patients, or the ones with wide pelvis, but can be easily addressed by increasing the length of the incision *(36)*.

In conclusion, AMIS is a safe, reproducible and rewarding technique which provides lower morbidity and faster postoperative recovery for the patient. Not only the aesthetic aspects (38) of the approach, but also the psychological ones (39) are predominant because the patients' well-being is rapidly restored.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Dixon T, Shaw M, Ebrahim S, Dieppe P. Trends in hip and knee joint replacement: socioeconomic inequalities and projections of need. Ann Rheum Dis 2004; 63:825-30.
2. Singh JA, Vessely MB, Harmsen WS, Schleck CD, Melton LJ 3rd, Kurland RL, Berry DJ. A population-based study of trends in the use of total hip and total knee arthroplasty, 1969-2008. Mayo Clin Proc 2010; 85:898-904.
3. Singh JA. Epidemiology of knee and hip arthroplasty: a systematic review. Open Orthop J 2011; 16:80-5.
4. Rachbauer F. Minimally Invasive total hip arthroplasty: anterior approach. Orthopäde 2006; 35:723-9.
5. Dorr LD, Maheshwari AV, Long WT. Early pain and functional results comparing minimally invasive to conventional total hip arthroplasty: A prospective, randomized blinded study. J Bone Joint Surg Am 2007; 89:1153-60.
6. Berger RA, Jacobs JJ, Meneghini RM, Valle CD, Paprosky W, Rosenber AG. Rapid Rehabilitation and recovery with minimally invasive total hip arthroplasty. Clin Orthop Relat Res 2004; 429: 239-47.
7. Smith-Petersen MN. Approach to and exposure of the hip joint for mold arthroplasty. J Bone Joint Surg Am 1949; 31A:40-6.
8. Judet J. Protheses en resine acrylic, Memoires de l Academie de Chirurgie. 1947; 73: 561.
9. Laude F. Total hip arthroplasty through an anterior Heuter minimally invasive approach. Interact Surg 2006; 1:5-11.
10. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am 1969; 51:737-55.
11. Light TR, Keggi KJ. Anterior approach to hip arthroplasty. Clin Orthop 1980; 152:255-60.
12. Matta JM, Shahrdar C, Ferguson T. Single-incision anterior approach for total hip arthroplasty on an orthopaedic table. Clin Orthop 2005; 441:115–24.
13. Andersson G. Hip assessment: a comparison of nine different methods. J Bone Joint Surg 1972; 54:621-5.
14. Berger RA: The technique of minimally invasive total hip arthroplasty using the two-incision approach. Instr Course Lect 2004; 53:149-55.
15. Foster DE, Hunter JR: The direct lateral approach to the hip for arthroplasty: advantages and complications. Orthopedics 1987; 10:274-80.
16. Hardinge K: The direct lateral approach to the hip. J Bone Joint Surg Br 1982; 64:17-9.
17. Harris WH: A new approach to total hip replacement without osteotomy of the greater trochanter. Clin Orthop Relat Res 1975; 106:19-26.
18. Vicar AJ, Coleman CR. A comaprison of the anterolateral, transtrochanteric, and posterior surgical approaches in primary total hip arthroplasty. Clin Orthop Relat Res 1984; 188:152–9.
19. van Stralen GM, Struben PJ, van Loon CJ. The incidence of dislocation after primary total hip arthroplasty using posterior approach with posterior soft-tissue repair. Arch Orthop Trauma Surg 2003; 123:219-22.
20. Baker AS, Bitounis VC. Abductor function after total hip replacement. An electromyographic and clinical review. J Bone Joint Surg Br 1989; 71:47-50.
21. DeWal H, Su E, DiCesare PE. Instability following total hip arthroplasty. Am J Orthop 2003; 32:377-82.
22. Barber TC, Roger DJ, Goodman SB, Schurman DJ. Early outcome of total hip arthroplasty using the direct lateral vs the posterior surgical approach. Orthopedics 1996; 19:873-5.
23. Jolles BM, Bogoch ER. Posterior versus lateral surgical approach for total hip arthroplasty in adults with osteoarthritis. Cochrane Database Syst Rev 2006; 19; 3: CD003828
24. Siguier T, Siguier M, Brumpt B. Mini-incision anterior approach does not increase dislocation rate: a study of 1037 total hip replacements. Clin Orthop 2004; 426:164–73.
25. Lowell TP. Single-Incision Direct Anterior Approach for Total Hip Arthroplasty Using a Standard Operating Table; J Arthroplasty 2008; 23 (Suppl 7):64-8.
26. Bhargava T, Goytia RN, Jones LC, Hungerford MW. Lateral femoral cutaneous nerve impairment after direct anterior approach for total hip arthroplasty. Orthopedics. 2010; 33:472.
27. Bal BS, Vallurupalli S. Minimally invasive total hip arthroplasty with the anterior approach. Indian J Orthop. 2008; 42:301-8.
28. Paillard P. Hip replacement by a minimal anterior approach. Int Orthop 2007; 31:13-5.
29. Laffosse JM, Chiron P, Accadbled F, Molinier F, Tricoire JL, Puget J. Learning curve for a modified Watson-Jones minimally invasive approach in primary total hip replacement: analysis of complications and early results versus the standard-incision posterior approach. Acta Orthop Belg 2006; 72:693-701.
30. Berry DJ, Berger RA, Callaghan JJ, Dorr LD, Duwelius PJ, Hartzband MA. Minimally invasive total hip arthroplasty development, early results, and a critical analysis. J Bone Joint Surg (Am) 2003; 85: 2235-46.
31. Jewett BA, Collis DK. High complication rate with anterior total hip arthroplasties on a fracture table. Clin Orthop Relat Res. 2011; 469: 503-7.
32. Kennon R, Keggi J, Zatorski LE, Keggi KJ. Anterior approach for total hip arthroplasty: beyond the minimally invasive technique. J Bone Joint Surg Am 2004; 86:91-7.
33. Kennon RE, Keggi JM, Wetmore RS, Zatorski LE, Huo MH, Keggi KJ. Total hip arthroplasty through a minimally invasive anterior surgical approach. J Bone Joint Surg Am. 2003; 85:39-48.
34. Rachbauer F. Minimally invasive total hip arthroplasty via direct anterior approach. Orthopade. 2005; 34:1103-10.

35. Aszmann OC, Dellon ES, Dellon AL. Anatomical course of the lateral femoral cutaneous nerve and its susceptibility to compression and injury. Plast Reconstr Surg 1997; 100:600-4.
36. Paillard P. Hip replacement by a minimal anterior approach. Int Orthop 2007; 31:13-5.
37. Yang L, Li HQ. Mini-incision joint replacement and minimally invasive joint surgery. Zhongguo Jiao Xing Wai Ke Za Zhi 2005; 13: 405–6.
38. Mow CS, Woolson ST, Ngarmukos SG, Park EH, Lorenz HP. Comparison of scars from total hip replacements done with a standard or a mini-incision. Clin Orthop Relat Res 2005; 441: 80–5.
39. Dorr LD, Thomas D, Long WT, Polatin PB, Sirianni LE. Psychologic reasons for patients preferring minimally invasive total hip arthroplasty. Clin Orthop Relat Res 2007; 458:94-100.

Minimalno invazivna artroplastika kuka: prednosti i mane

Božidar Šebečić, Mario Starešinić, Vencel Čuljak, Mladen Japjec
Zavod za traumatologiju, Klinika za kirurgiju, Klinička bolnica Merkur, Zagreb, Hrvatska

SAŽETAK

Cilj Prikazati metodu minimalno invazivnog prednjeg pristupa na kuk u liječenju koksartroze i prijeloma kuka, te njene prednosti.

Metode Tokom 2008. i 2009. godine, minimalno invanzivnom metodom operirano je 35 pacijenata. Oni su uspoređeni s 35 pacijenata operiranih u istom periodu lateralnim, transglutealnim pristupom (kontrolna grupa). Sve operacije izveo je isti kirurški tim. Glavni razlog operacija bila je koksartroza, dok su dva pacijenta u grupi s minimalno invazivnim pristupom imala frakturu vrata femura. Rane postoperativne komplikacije i funkcionalni status praćen je s Haris hip bodovanjem (HHS).

Rezultati U odnosu na kontrolnu skupinu u AMIS grupi operacije su bile kraće, s manjim gubitkom krvi (78 min i 490 ml, odnosno 85 min i 570 ml). U AMIS grupi, kod jednog pacijenta došlo je do pojave postoperativne koljene boli, frakture velikog tuberkula, prekomjernog frezanja acetabula, perforacije femura frezom, te kod dva pacijenta lezije *n. cutaneus femoralisa lat.* Nije bilo infekcije i luksacije, za razliku od kontrolne skupine u kojoj je u jednom slučaju došlo do postoperativne luksacije, te kod dva pacijenta do površinske infekcije. Pacijenti operirani minimalno invazivnim pristupom bili su zadovoljniji, tražili su manje analgezije i njihova je rehabilitacija bila kraća. Haris hip bod (HHS) u AMIS grupi, nakon dva mjeseca, iznosio je 80,2, a u kontrolnoj 69,4; nakon četiri mjeseca, u AMIS grupi iznosio je 92,4, a u kontrolnoj 88,1.

Zaključak AMIS je sigurna, izvediva i zahvalna metoda koja osigurava niski morbiditet i brzi postoperativni oporavak pacijenata.

Ključne riječi: minimalno invazivno, prednji pristup, kuk, artroplastika

NOTES

Retrospective study of total hip arthroplasty in Brod-Posavina and Požega-Slavonia counties in 2010

Tomislav Crnković[1], Dragutin Bitunjac[2], Hrvoje Pitlović[2], Dalibor Marić[3]

[1]Department of Orthopedic Surgery, General County Hospital, Požega, [2]Department of Orthopedic Surgery, General Hospital "Dr. Josip Benčević", Slavonski Brod, [3]Department of Orthopedic Surgery, General Hospital, Nova Gradiška; Croatia.

Corresponding author: Tomislav Crnković; Department of Orthopaedic Surgery, General County Hospital; Osječka 107, 34 000 Požega, Croatia; Phone: +385 34 254461; fax.: +385 34 271713; Email: tomislav_crnkovic@inet.hr

Original submission: 12 September 2011; **Accepted**: 23. September 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):166-168

ABSTRACT

The aim of this retrospective study is to present the incidence of total hip arthroplasty (THA) in Brod-Posavina and Požega-Slavonia counties in 2010 along with an analysis of post-operative complications. The research was carried out at orthopaedic departments in three hospital institutions, "Dr. Josip Benčević "Slavonski Brod General Hospital, the Nova Gradiška General Hospital and the Požega General County Hospital. A total of 27 849 patients was examined in orthopedic outpatient clinics, 1 457 surgical procedures were conducted, of which 239 (16.40%) were THA. There were five (2.09%) dislocations of endoprosthesis, one case (0.42%) of endoprostheses infection, whereas none of periprosthetic fractures and peroneal nerve palsy were presented.

Key words: total hip arthroplasty, Brod-Posavina, Požega-Slavonia, county

INTRODUCTION

Total hip arthroplasty (THA) assumes today a significant amount of daily orthopedic routines (1). It is estimated that around 15-20 % of all orthopedic operations in the world involve the total hip replacement, and when compared to the number of implanted endoprosthesis for large joints, arthroplasty of hip joint is most common (2).

The fundamental goal of this paper is to present the incidence of THA in the two Croatian counties in 2010 along with an analysis of post-operative complications. No data were published about THA incidence in these regions including entire Croatia and neighbouring countries. We believe that the presented data could be used by orthopedic surgeons to compare their results of THA with those from different regions.

PATIENTS AND METHODS

The retrospective study was carried out at orthopaedic departments in three hospitals within Brod-Posavina and Požega-Slavonia Counties, which otherwise conduct hip joint endoprothetics, "Dr. Josip Benčević " Slavonski Brod General Hospital, Nova Gradiška General Hospital and Požega General County Hospital. The two neighbouring and well-tied counties in central and eastern Croatia comprise 5.9% of the country's total population. According to the Census from 2001, Požega-Slavonia County has 85 831 inhabitants representing 1.9% of the population in the Republic of Croatia, while Brod-Posavina County has 176 765 inhabitants or 4% of the county's total population (Croatian Bureau of Statistics, 2001).

Data from 2010 were collected and analysed concerning the number of patients who belong to the area covered by orthopedic outpatient clinics, number of examinations, surgical procedures, THAs, number of complications (infection, dislocation, nerve palsy, periprosthetic fracture) and number of orthopedic surgeons per hospital.

The data were analysed using a descriptive method along with standard statistical methods and are presented in two tables.

RESULTS

A research in the two counties involved a total of 27 849 patients examined in orthopedic outpatient clinics during 2010. With regard to surgical procedures 1 457 orthopedic procedures were conducted, of which 239 (16.40%) were THA, 96 (40.32%) patients being male and 143 (59.68%) female. Indications for operative procedures in 221 (92.47%) cases included osteoarthritis of the hip, and in 18 cases (7.53%) femoral neck fracture. An average age of surgically treated patients was 67.8. A total of 226 (95%) patients underwent procedures for non-cemented implants whereas only 13 (5%) cases involved cemented implants.

Table 1. Number of patients, examinations, surgical procedures, THA and surgeons per hospital in 2010*

	The number (%)				
	Patients gravitating towards orthopedic outpatient clinics	Examinations in orthopedic outpatient clinics	Orthopedic surgeons per institution	Surgical procedures	THA
"Dr. Josip Benčević" Slavonski Brod General Hospital	160000	15000	4	832	126 (15.14%)
Nova Gradiška General Hospital	6500	4200	1	260	45 (17.31%)
Požega General County Hospital	80000	8649	3	365	68 (18.63%)

*THA, total hip arthroplasty

Table 2. Complications relating to THA per hospital in 2010

	The number (%)			
	Dislocation	Infection	Peroneal nerve palsy	Periprosthetic fractures
"Dr. Josip Benčević" Slavonski Brod General Hospital	3 (2.38%)	1 (0.79%)	0	0
Nova Gradiška General Hospital	0	0	0	0
Požega General County Hospital	2 (2.94%)	0	0	0

When considering complications, the most common was endoprosthesis dislocation. When compared to a total of 239 THAs, there were five dislocations representing 2.09% of implant dislocations. One case (0.42 % of total procedures) of infection was recorded, whereas periprosthetic fractures and peroneal nerve palsy were not presented in any of the cases (Tables 1 and 2).

DISCUSSION

It is indisputable that the rising trend in the number of THA in the world is closely related to the development and improved design of implants and surgical procedures (3, 4). Only within the USA in 2006, there was an estimate of 900 000 hip and knee arthroplasties, and based on some estimates this number will grow to four million by 2030 (5, 6). Along with positive results such as pain relief, improved hip joint functioning and increased quality of life for patients, a percentage of hip joint endoprosthesis may result in particular problems. The most common complication following total hip arthroplasty was endoprosthesis dislocation (2). This complication occurs in 1-3% of cases of primary THA, whereas for revision hip arthroplasty this percentage increases significantly to around 15-20% (2). Improvements in surgical techniques, perioperative routines and prophylactic measures have reduced the incidence of infection from 5-10% in late 1960s to around 1% today (7). The incidence of periprosthetic femoral fractures after hip arthroplasty is increasing as a result of the incresed performance of THA, the aging population and complications such as osteolysis and aseptic loosening (8). Development of a peripheral nerve palsy after THA is uncomon but potentially devastating complication (9).The reported incidence of peroneal nerve injury in THA ranges from 0.3% to 2.1% (9). Lengthening of 2.7 cm increased the risk of injury to the peroneal division, whereas lengthening of 4.4 cm increased risk of the entire sciatic nerve (10).

In our case we had 2.09% of dislocation of primary THA and 0.42% of endoprosthesis infections. Neurological complications as well as periprosthetic fractures were not evident in our study.

In conclusion, the results of this research conducted on patients in the two respective counties in the Republic of Croatia are within the limits cited in the relevant international literature, and the percentage of post-operative complications falls within the range cited in other similar researches.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Aghayev E, Beck A, Staub LP, Dietrich D, Melloh M, Orljanski W, Röder C. Simultaneous bilateral hip replacement reveals superior outcome and fewer complications than two-stage procedures: a prospective study including 1819 patients and 5801 follow-ups from a total joint replacement registry. BMC Musculoskelet Disord 2010; 11:245.
2. Smerdelj M, Orlic D, Bergovec M. Emergencies in total hip replacement. Lijec Vjesn 2005; 127:189-93.
3. Singh JA. Epidemiology of knee and hip arthroplasty: a systematic review. Open Orthop J. 2011; 5:80-5.

4. Kolundzic R, Orlic D. Particle disease-aseptic loosening of the total hip endoprosthesis. Lijec Vjesn 2008;130:16-20.
5. Nwachukwu BU, Kenny AD, Losina E, Chibnik LB, Katz JN. Complications for racial and ethnic minority groups after total hip and knee replacement: a review of the literature. J Bone Joint Surg Am 2010; 92:338-45.
6. Singh JA, Vessely MB, Harmsen WS, Schleck CD, Melton LJ 3rd, Kurland RL, Berry DJ. A population-based study of trends in the use of total hip and total knee arthroplasty, 1969-2008. Mayo Clin Proc 2010; 85:898-904.
7. Dale H, Hallan G, Hallan G, Espehaug B, Havelin LI, Engesaeter LB. Increasing risk of revision due to deep infection after hip arthroplasty. Acta Orthop 2009; 80:639-45.
8. Park SK, Kim YG, Kim SY. Treatment of periprosthetic femoral fractures in hip arthroplasty. Clin Orthop Surg 2011; 3:101-6.
9. Brown GD, Swanson EA, Nercessian OA. Neurologic injuries after total hip arthroplasty. Am J Orthop 2008; 37:191-7.
10. Edwards BN, Tullos HS, Noble PC. Contributory factors and etiology of sciatic nerve palsy in total hip arthroplasty. Clin Orthop Relat Res 1987; 218:136-41.

Retrospektivna studija totalnih aloartroplastika zgloba kuka u Brodsko-posavskoj i Požeško-slavonskoj županiji za 2010. godinu

Tomislav Crnković[1], Dragutin Bitunjac[2], Hrvoje Pitlović[2], Dalibor Marić[3]

[1]Ortopedski odjel, Opća županijska bolnica, Požega; [2]Ortopedski odjel, Opća bolnica „Dr. Josip Benčević“, Slavonski Brod; [3]Ortopedski odjel, Opća bolnica, Nova Gradiška; Hrvatska

SAŽETAK

Cilj ove retrospektivne studije je prikazati učestalost totalnih aloartroplastika zgloba kuka na području Brodsko-posavske i Požeško-slavonske županije za 2010. godinu, uz analizu postoperacijskih komplikacija. Istraživanje je provedeno na ortopedskim odjelima tri bolničke ustanove (Opća bolnica “Dr. Josip Benčević” Slavonski Brod, Opća bolnica Nova Gradiška, Opća županijska bolnica Požega). U ortopedskim ambulantama pregledano je ukupno 27.849 pacijenata, te učinjeno 1.457 ortopedskih zahvata, od čega su 239 (16,40%) bili totalne endoproteze zgloba kuka. Pronađeno je pet (2,09%) luksacija kuka, jedan slučaj (0,42%) infekcije endoproteze, dok periprostetički prijelomi i pareze *n. peroneusa* nisu pronađene ni u jednom slučaju.

Ključne riječi: totalna aloartroplastika kuka, Brodsko-posavska županija, Požeško-slavonska županija.

CASE REPORT

Total hip arthroplasty in avascular necrosis of the femoral head in a patient with transplanted heart

Ivan Samardžić[1], Jure Samardžić[2,3], Davor Miličić[2,3], Robert Kolundžić[4]

[1]Deparpement for Orthopaedic Diseases, General Hospital “Dr. Josip Benčević“ Slavonski Brod, [2]University of Zagreb, School of Medicine, [3]Department for Cardiovascular Diseases, Clinical Hospital Center Zagreb, [4]Clinic for Traumatology, Clinical Hospital Center “Sestre Milosrdnice“, Zagreb; Croatia

Corresponding author: Ivan Samardžić, Deparpement for Orthopaedic Diseases, General Hospital “Dr. Josip Benčević“; Nikole Tesle 4, 35 000 Slavonski Brod; Phone: +385 35 410 042; E-mail: isamar@net.hr

Original submission: 17 October 2011; **Accepted** 14 November 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):168-171

ABSTRACT

With the improvement of transplantation techniques and immunosupresive treatment of transplanted patients, the number of heart transplantations increases worldwide including Croatia. The survival of such patients is significantly increased. Therefore, the prevalence of known complications is high, one of which is avascular necrosis of the femoral head. This paper presents a case of the first patient in Croatia who underwent bilateral hip arthroplasty due to bilateral avascular necrosis of the femoral head as a side effect of corticosteroid therapy after heart transplantation.

Key words: total hip arthroplasty, avascular necrosis, femoral head, heart transplantation

INTRODUCTION

Heart transplantation is an operative procedure in which recipient’s heart is replaced with a heart of a suitable donor (1). It is mostly used in the treatment of end-stage heart failure refractory to medicament therapy with recepient’s life expectancy less than one year (1). Avascular necrosis of the femoral head (AVN) has been described and recognized as a complication in patients after transplantation of solid organs (2). It is believed that long-term corticosteroid therapy as a part of immunosuppressive therapy causes avascular necrosis (3). Advances in surgical techniques and technology, improvement

in immunosuppressive therapy and better screening of patients has increased the survival rate of transplanted patients because of which the prevalence of avascular necrosis of the femoral head is predicted to increase as well (1). Avascular necrosis of the femoral head is a pathological process that occurs due to disrupted blood supply of the bone and the resulting ischemia leads to necrosis of bone mass and osteocites, which usually ends with the collapse of the necrotic bone (3).

CASE REPORT

A 64-year-old male visited the orthopedic clinic because of intensive pain and limited movements in both hips. Six months before the arrival to orthopedic clinic he began experiencing pain in the left hip during walk, which progressed with time. Later he began experiencing pain in the right hip as well. He moved with crutches and help of other people, and at the time of examination mostly in a wheelchair. The pain was present during the rest and also at night.

Two years earlier the patient had undergone orthotopic heart transplantation because of severe end-stage chronic heart failure due to dilated cardiomyopathy. After the heart transplantation the patient received long-term triple immunosuppressive therapy, which included glucocorticoids , besides cyclosporine and mycophenolat-mophetil. In addition to bilateral aseptic necrosis of the femoral head the patient also developed other steroid side-effects such as lumbar spine osteoporosis and iatrogenic diabetes mellitus. He was also treated for arterial hypertension, hyperlipidemia and hyperuricemia. The patient was in regular cardiologist's control who was of the opinion that the perioperative risk for hip arthroplasty was increased but acceptable.

In time of the orthopedic examination the patient was practically immobile. He developed hypotrophy of hip musculature and movements of both hips were severely limited and painful. Clinically measured, a discrepancy in the length of the lower extremities was not found. X ray of both hips showed bilateral aseptic necrosis of the femoral head resulting in severe osteoarthritis (Figure 1). Surgical treatment of both hips with a total hip prosthesis was indicated.

After preoperative measures and preparation of the patient, a surgical procedure of total arthroplasty of the right hip was preformed first. A cementless prostheses with metal head and polyethylene insert was implanted (Figure 2 A). Rehabilitation was complicated with one episode of prosthesis luxation on the19th postoperative day, which demanded reposition. A coxofemoral orthosis was applied after reposition.

Six months later he underwent a total arthroplasty of the left hip with the same prosthesis model. Postoperative follow-up and rehabilitation were uneventful (Figure 2 B). During the follow-up of 29 months after the second operation there were no clinical and radiological signs of instability of either prostheses. The patient was independently mobile and able to perform daily activities without significant pain. He regularly attends the orthopedic and cardiologist's controls.

In Croatia, the number of patients with heart transplant increases every year. In the period from 1998 to 2006 in the Clinical Hospital Center Zagreb 81 heart transplants were performed (18

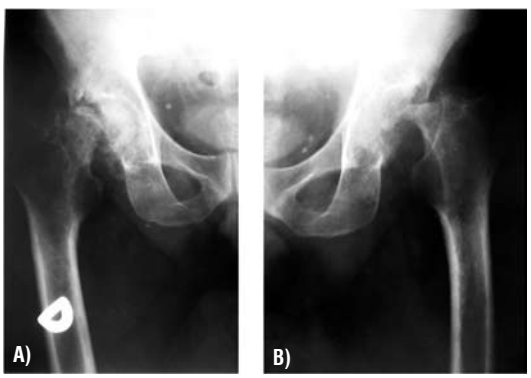


Figure 1. X- ray images of both hips showing bilateral aseptic necrosis of the femoral head resulting in severe osteoarthritis of A) right hip, B) left hip (Samardžić I., 2008)

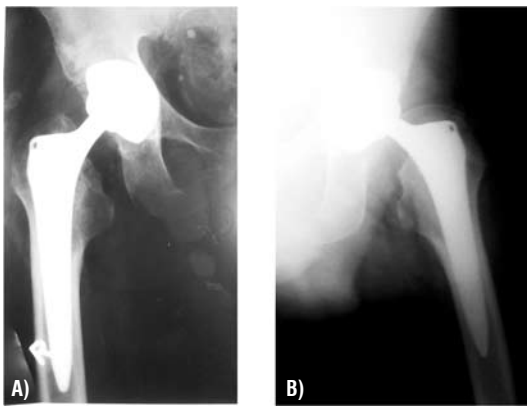


Figure 2. Figure 2. X- ray imaging after total hip arthroplasty A) right hip, B) left hip (Samardžić I., 2009)

heart transplantations of the total 36 in Croatia were performed during in 2010) (4,5). The prevalence of avascular necrosis of the femoral head in patients with transplanted heart, according to the available medical literature was 3-40% (6,7). This is the first reported case of bilateral total hip arthroplasty in patients with heart transplant in Croatia and it is expected that the number of such patients will increase (4-7).

There are few publications on this subject, however, the small number of papers published so far have shown good results. Burton et al. (8) in 1977 have published a presentation of two cases of bilateral total hip arthroplasty after heart transplant. Ison et al. (6) in 1986 published an article where they have shown excellent results after total hip arthroplasty of 9 patient who had bilateral hip arthroplasty due to AVN after heart transplantation. No patient required revision, and radiological control showed no signs of instability of prostheses during follow-up (6). Furthermore, they showed that the incidence of complications in patients with transplanted heart is not significantly different from patients who did not undergo heart transplantation (5). In 2007 Leon et al. (9) reported on a sample of 249 patients after heart transplantation, AVN incidence of 7.2% (18 patients). Total hip arthroplasty was preformed after an average of 27 months after the heart transplantation, depending on the patients' clinical feature and symptoms tolerance (9). The average age of patients at the time of arthroplasty was 52 (9). They also showed very good functional (HHS and WOMAC score) and radiological results (9). At the average follow-up period of 35.4 months they found no signs of instability, implant migration, dislocation or periprosthetic fractures (9). No revision had to be made (9). The most common complication was heterotopic ossification (15.8%), which did not significantly affect the hip function. Specified complication, as the most frequent was also described by other authors (6).

Application of both cemented and cementless prosthesis in previously published articles have shown good results. Some authors have used cemented prosthesis (6,8) mainly due to osteopenia in transplant patients and impaired osteogenesis caused by glucocorticoid therapy which would presumably lead to lower bone ingrowth and consequently migration and instability of cementless prosthesis. Other authors, however, used cementless prosthesis (9) primarily because the patients were younger at the time of surgery. It was shown that there were no signs of instability of the cementless prosthesis in those patients, which shows that corticosteroid therapy does not compromise the implant integration into the bone, despite the fact that corticosteroids cause inhibition of osteogenesis (9).

Total hip arthroplasty in patients after heart transplantation have excellent clinical and radiological results, and despite the increased perioperative risk in immunocompromised patients, total hip arthroplasty appears to be safe and effective method of treatment of femoral head AVN.

FUNDING

No specific funding was received for this study

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Donald M Botta. Heart transplantation. http://emedicine.medscape.com/article/429816-overview (26. 10. 2011).
2. Elmstedt E, Svahn T. Skeletal complications following renal transplantation. Acta Orthop. Scand. 1981; 52:279-86.
3. Kenneth J, Koval. Orthopaedic knowledge update 7: home study syllabus. 2nd ed. Amer Acad of Orthopaedic Surgeons, 2002.
4. Ćorić V, Miličić D, Gašparović H, Rajsman G, Širić F, Jelić I. Eighteen years of heart transplantation – a single center experience. Coll Antropol 2006; 30:909-13.
5. Samardžić J, Lovrić D, Miličić D. Transplantacija srca – indikacije, kontraindikacije I dugoročno liječenje transplantiranih bolesnika. Medix 2011; 92/93:160-4.
6. Isono SS,Woolson ST, Schurman DJ. Total joint arthroplasty for steroid-induced osteonecrosis in cardiac transplant patients. Clin Orthop 1987; 217:201-8.
7. Marston SB, Gillingham K, Bailey RF, Cheng EY. Osteonecrosis of the femoral head after solid organ transplantation : a prospective study. J Bone Joint Surg 2002; 84-A: 2145-51.
8. Burton DS, Mochizuki RM, Halpern AA. Total hip arthroplasty in the cardiac transplant patient. Clin Orthop 1978; 130:186-90.
9. José Luis León, Carlos Resines, Alberto Zafra. Total hip arthroplasty in heart transplant patients. Acta Orthop Belg 2007; 73:720-8

Totalna artroplastika kukova zbog avaskularne nekroze glave femura kod bolesnika s transplantiranim srcem

Ivan Samardžić[1], Jure Samardžić[2,3], Davor Miličić[2,3], Robert Kolundžić[4]

[1]Odjel za ortopedske bolesti "Dr. Josip Benčević" Slavonski Brod; [2]Medicinski fakultet Sveučilišta u Zagrebu; [3]Klinika za bolesti srca i krvnih žila, Klinički bolnički centar Zagreb; [4]Klinika za traumatologiju, Klinički bolnički centar "Sestre milosrdnice", Zagreb; Hrvatska

SAŽETAK

Zahvaljujući napretku u transplantacijskoj tehnici i imunosupresivnoj terapiji, broj transplantacija srca povećao se kako u svijetu, tako i u Hrvatskoj. Broj preživjelih bolesnika znatno je povećan, a s tim i prevalencija poznatih komplikacija, od kojih je jedna i avaskularna nekroza glave femura. U ovom članku prikazan je slučaj bolesnika koji je prvi u Hrvatskoj liječen obostranom artroplastikom kukova zbog avaskularne nekroze glave femura, kao posljedice liječenja kortikosteroidima nakon transplantacije srca.

Ključne riječi: potpuna artroplastika kuka, avaskularna nekroza, glava femura, transplantacija srca

CASE REPORT

Use of multislice computed tomography in radiological treatment of patients with hip pathology

Bilal Imširović[1], Bekir Karčić[1], Besima Hadžihasanović[2], Tarik Kapidžić[3], Enver Zerem[4], Ibrahim Omerhodžić[5]

[1]Department of Radiology, Cantonal Hospital Zenica, Zenica, [2]Department of Radiology, Clinical Center of the University of Sarajevo, Sarajevo, [3]Department of Orthopedics and Traumatology, Cantonal Hospital Zenica, Zenica, [4]Department of Internal Diseases, University Clinical Center, Tuzla, [5]Department of Neurosurgery, Clinical Center of the University of Sarajevo, Sarajevo; Bosnia and Herzegovina

Corresponding author: Bilal Imširović; Department of Radiology, Cantonal Hospital Zenica; Crkvice 67, 72000 Zenica, Bosnia and Herzegovina; Phone: +387 32 405 133; fax.: +387 32 405 534; E-mail: bilal_imsirovic@yahoo.com

Original submission: 05 July 2011; **Accepted**: 27 September 2011.

Med Glas Ljek komore Zenicko-doboj kantona 2012; 9(1):171-173

ABSTRACT

In this paper we are presenting the application of Multislice CT Scan (MSCT) as a part of radiological treatment in a female patient with avascular necrosis of head and neck of the right femur, which ocurred as a consequence of developmental hip dysplasia. The left hip joint of the patient was previously replaced by a prosthetic implant.

Key words: developmental dysplasia, hip, avascular necrosis, artificial prosthesis, MSCT

INTRODUCTION

Developmental disorder of the hip (developmental dysplasia of the hip, DDH) includes a spectrum of anatomical abnormalities of the hip joint that occur during child's development resulting in non-conforming joints, which usually has a consequence in avascular necrosis (AVN) of the head of femur (1,2). Despite the fact that DDH is uncommon, AVN is a relatively common disease. The diagnosis of DDH may be made clinically and by ultrasound, while the diagnosis of AVN is confirmed only by radiological imaging (3). According to the current findings, 9-10% of all hip prosthetic implantations have interference with the maturation of the hip (4).

CASE REPORT

A forty-nine-year-old female patient, who had increasing *problems with moving* as well as clinical signs of pronounced pain in the right hip, was sent for CT examination of both coxofemoral joints during the diagnostic examination and preoperative evaluation for the right *hip replacement surgery*. From the previous medical records, information was obtained that the patient had inborn dislocation of both hips and the left hip joint had been replaced by a prosthetic implant five years ago (Plasmacup, polimetilen inlay, Aesculap bicontact s and sd). It was performed due to aseptic osteonecrosis of the femur head based on congenital dysplasia.

Multislice 3DCT scan with axial, multiplanar reformation (MPR) and shaded surface display (SSD) reconstruction (SIEMENS SOMATOM Definition AS, Erlangen, Germany) of pelvis and hips was performed and it revealed that the right coxofemoral joint was exceptionally altered, with deformed acetabulum that had a steep roof,

and the presence of bone apposition to the lateral edge. It also had uneven contours with visible signs of marked subchondral sclerosis and presence of subchondral cysts. Femur was elevated (cranialized). Great trochanter of the femur was approximately 35 mm above the joint level, located in glutean musculature. The head and neck of the femur were resorbed. Intraarticular space was expanded. At the medial edge of the femur, on the level of the small trochanter, and towards the caudal, there was a visible bone fragment about 30 mm long, with the largest diameter of 15x5 mm. In the area of the left coxofemoral joint, the state after implantation of prosthesis with a marked bony apposition at the edge of acetabulum was visible (*Figures 1 and 2*).

Avascular necrosis (aseptic osteonecrosis, bone infarction, aseptic ischemic bone necrosis, *necrosis aseptica ossium*) is a bone disease caused by circulatory disorders, which occurs due to the insufficient bone supply with blood and consecutive necrosis (3). Experience has shown that AVN of the femur head may occur as a result of numerous atraumatic and traumatic factors, where the leading traumatic etiological factor is luxation of the femur head (5). In the early stages of AVN, the disease is asymptomatic, but during the time bone and surrounding structures decay and pain is more intensive (3)**.** Due to the lack of objective parameters of the disease, patients often do not realize it is serious, and it is diagnosed with a large delay. Then, the installation of artificial hip prosthesis is inevitable, and definitive surgical treatment entails the use of a total endoprosthesis (TEP) (6).

Patients with pain in the hip should have a valid physical examination. It is important to try to distinguish whether the underlying symptoms are of a neurogenic, vascular, or musculoskeletal nature. This is the key for further diagnostic evaluation (7). Radiological methods are the gold standard for the diagnosis of AVN of the bone (3,8). MSCT provides the three-dimensional view of bone and shows changes in bones with much clearer differentiation of structures in relation to standard radiography (3).

Although this issue is not new, osteonecrosis is still classified as an unresolved problem in orthopedics (9). Unfortunately, in practice, from time to time, it appears in some patients with AVN in late stages and the radiologist is requested to do a CT scan, as a part of the preoperative evaluation. Because of absence of an early diagnosis and treatment of primary disease in the presented case, the result was disabled and seriously distorts the quality of life of the evaluated patient. There is a need to pay attention to timely diagnostic testing of conditions that can lead to AVN. When AVN is suspected cli-

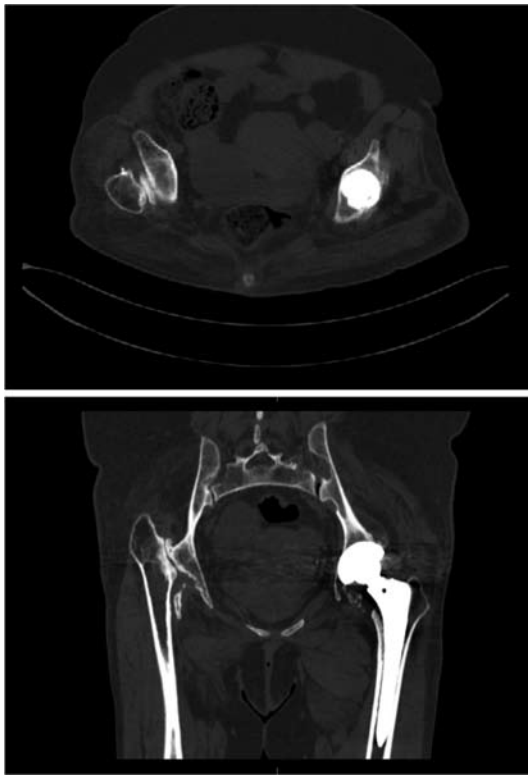


Figure 1. Pelvic CT scans of hips, axial and coronal section: AVN of head and neck of the right femur with prosthetic implant on the left hip (Department of Radiology, Cantonal Hospital Zenica, 2010)

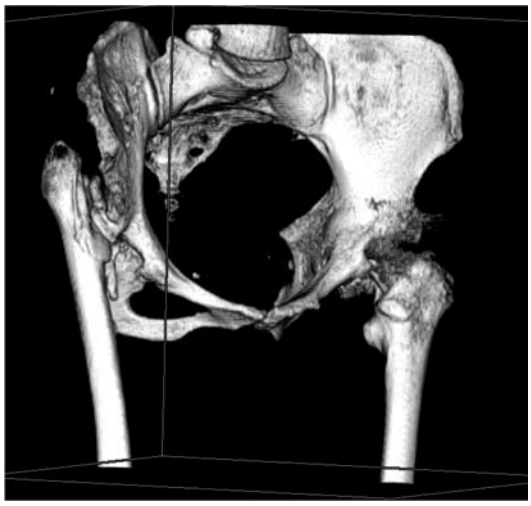


Figure 2. The same patient as on Figure 1. Pelvic CT scans of the hips, SSD reconstruction: AVN of the head and neck of the right femur with prosthetic implant on the left hip (Department of Radiology, Cantonal Hospital Zenica, 2010)

nically with normal radiographs, further evaluation is needed. MRI of hips without contrast is the most sensitive and specific method of establishing or excluding AVN (10), but our case points out that MSCT, especially in neglected, serious forms, has an important role in the diagnostics. It may be useful for surgical planning of osteotomy by defining anatomic localization of the AVN and the extent of bone deformity. MSCT may show subchondral fracture not seen on MRI, and it is also important if MRI is not available or is contraindicated (10).

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATIONS

Competing interests: none to declare.

REFERENCES

1. Shahryar N, Masood U, Kamran H, Haq N. Developmental dysplasia of the hip. Orthop Rev (Pavia) 2010; 23:2: e19.
2. Segal LS, Boal DK, Borthwick L, Clark MW, Localio AR, Schwentker EP. Avascular necrosis after treatment of DDH: the protective influence of the ossific nucleus. J Pediatr Orthop. 1999; 19:177-84.
3. Cicin-Sain Bajraktarević T, Bergovec M. Diagnostic procedures in patients with bone aseptic necrosis. In: Zbornik radova, Aseptične nekroze kosti, Hrvatska znanstvena bibliografija, Zagreb, Croatia, 2007. Available on: http://bib.irb.hr/prikazi-rad?&rad=386633. (23 September 2011)
4. Graf R, Farkas P, Lercher K, Tschauner C, Lojpur M. Manual for hip sonography. Stolzalpe, Austria: Stolzalpe, 1999.
5. Roeder LF Jr, De Lee JC. Femoral head fractures associated with posterior hip dislocation. Clin Orthop Relat Res 1980; 147:121-30.
6. Jeremic D, Nikolic D, Ilic S, Draskovic V. Early results of cementless hip arthroplasty in the treatment of femoral head posttraumatic and atraumatic osteonecrosis. Vojnosanit preg 2005; 62:513-7.
7. Lequesne M, Zaoui A. Misleading "hip" or buttock pain: proximal arteritis or lumbar spinal stenosis?. Presse Med. 2006; 35(4 Pt 2):663-8.
8. Dalagija F, Lincender L, Beslic S, ed. Diagnostic radiology. Guide. Sarajevo, Association of Radiologists in BiH, 2008.
9. Drescher W, Pufe T, Smeets R, Eisenhart-Rothe RV, Jäger M, Tingart M. Avascular necrosis of the hip - diagnosis and treatment. Z Orthop Unfall 2011; 149:231-40.
10. Seeger LL, Daffner H, Weissman BN, Arnold E, Bancroft L, Bennett DL, et al. Avascular Necrosis (Osteonecrosis) of the Hip. ACR Appropriateness Criteria. American College of Radiology, 2009. http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonMusculoskeletalImaging/AvascularnecrosisoftheHipDoc3.aspx. (23 September 2011)

Primjena višeslojne kompjuterizirane tomografije u radiološkoj obradi bolesnika s patologijom kuka

Bilal Imširović[1], Bekir Karčić[1], Besima Hadžihasanović[2], Tarik Kapidžić[3], Enver Zerem[4], Ibrahim Omerhodžić[5]

[1]Služba za radiologiju, Kantonalna bolnica Zenica, Zenica; [2]Klinika za radiologiju, Klinički centar Univerziteta u Sarajevu, Sarajevo; [3]Služba za ortopediju i traumatologiju, Kantonalna bolnica Zenica, Zenica; [4]Interna klinika, Univerzitetski klinički centar Tuzla, Tuzla; [5]Klinika za neurohirurgiju, Klinički centar Univerziteta u Sarajevu, Sarajevo; Bosna i Hercegovina

SAŽETAK

U radu je prikazana primjena višeslojnog CT aparata (MSCT) u radiološkoj obradi bolesnice kod koje je nastala avaskularna nekroza glave i vrata desne bedrene kosti, kao posljedica razvojnog poremećaja kuka, pri čemu je bolesnica na lijevom kuku imala od ranije ugrađen umjetni zglob.

Ključne riječi: razvojni poremećaj, kuk, avaskularna nekroza, umjetni zglob, MSCT