




Effect of Pre-Emptive Paracetamol Infusion on Postoperative Analgesic Consumption in Children Undergoing Elective Herniorrhaphy

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Objective: Studies have suggested that pre-emptive analgesia may decrease postoperative pain and opioid consumption. This study was undertaken to determine whether pre-emptive analgesia reduces postoperative pain and total paracetamol and opioid consumption in children undergoing herniorrhaphy.

Methods: In this retrospective study, medical records were analysed before and after the pre-emptive analgesia regimen was introduced. Demographic data, perioperative drug consumption and discharge time were recorded. In the first group, no pre-emptive analgesia (NA; year, 2011; n=60) was given and in the second group, the pre-emptive analgesia (PA) paracetamol 10-15 mg kg⁻¹ was given intravenously in the surgical ward at least 1 h before the surgical procedure (year 2013; n=60). Postoperative pain determining supplemental pain medications was scored using a Faces Pain Scale or visual analogue scale. Total paracetamol and opioid consumption during 24 perioperative hours was registered for all patients. The statistical analysis was performed using t test and Chi-square test.

Results: The mean age of children was 69.6±49.9 and 58.7±32.4 months (p=0.157), and the mean body mass index (BMI) was 18.3±8.8 kg m⁻² and 16.4±3.7 kg m⁻² (p=0.125) in the NA and PA groups, respectively. Total paracetamol consumption was 1157.8±908.8 mg vs. 983.0±536.4 mg (p=0.202), and the total opioid consumption was 5.8±4.7 in the NA group and 7.0±4.6 morphine equivalents in the PA group (p=0.160). No differences in the discharge time between the groups were observed (2.1±0.3 vs. 2.0±0.3 days, p=0.13).

Conclusion: PA was proven to be efficient in the terms of postoperative pain control but did not reduce the overall analgesic drug consumption in the children undergoing elective herniorrhaphy. Multimodal pain treatment may decrease the consumption of analgesic drugs.

Keywords: Pain, postoperative, paracetamol, analgesics, herniorrhaphy, outcome

Introduction

Inguinal hernia is the most common condition in children requiring surgical intervention (1, 2). Postoperative pain after herniorrhaphy is common and presents diagnostic and therapeutic challenges. According to the International Association for the Study of Pain, pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (3).

Pre-emptive analgesia is the administration of analgesic drugs before surgical incision for preventing the establishment of central sensitisation caused by incisional injury and inflammatory response (4, 5). It was first introduced by Wall in 1988 (6). Paracetamol is potentially the most useful nonopioid drug for acute pain treatment in children. Intravenous paracetamol is widely used to relieve mild to moderate postoperative pain. Also, it is well tolerated and relatively free of side effects in clinical doses. The aim of this retrospective study was to analyse the impact of pre-emptive parenteral paracetamol analgesia on postoperative analgesic drug consumption.

Methods

After the institutional ethics committee approval was received for this study from the ethics committee of Osijek University Hospital (No. 22512-2/2015), this retrospective study was conducted in the department of paediatric surgery in the tertiary University Hospital Osijek. Preemptive analgesia regimen was introduced in 2012. All children undergoing elective

hernia repair after 2012 were given paracetamol 10-15 mg kg⁻¹ intravenously in the surgical ward at least 1 h before the surgery. Their parents have signed informed consent for both anaesthesia and the surgical procedure.

In this retrospective cohort study, drug consumption in two patients' groups was compared: patients who received no pre-emptive analgesia (NA group; n=60, year 2011) with pre-emptive analgesia group (PA group, n=60, year 2013). After thiopental induction, balanced sevoflurane in nitrous oxide anaesthesia was administered with intraoperative fentanyl, alfentanil or sufentanil boluses according to the patient's body mass, pulse and blood pressure measurements. Controlled mechanical ventilation was performed using a laryngeal mask to maintain normal peripheral haemoglobin saturation and normocarbida.

In the NA group, the first paracetamol dose was given intravenously at the end of surgery before skin closure and was registered in the anaesthetic chart.

Standard doses of paracetamol were prescribed by the paediatric surgeon at 8-h intervals. Postoperative pain requiring supplemental medications was rated using a Faces Pain Rating Scale, where 0 indicated no pain and 10 indicated 'hurts as much as possible'. It was assessed in the recovery room by an attending anaesthesiologist or a paediatric surgeon in the surgical ward. Depending on the patient's pain expression, pain scores were registered. Children whose pain was rated as ≤4 were given paracetamol and those rated as ≥5 were given opioids. Meperidine, pentazocine or tramadol were the opioid medications used. For intergroup comparisons, the morphine equivalent was calculated (7). Children who expressed no pain were given no analgesic medications.

Demographic data, total paracetamol, opioid consumption and discharge time for both groups were registered.

Statistical analysis

The statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) 22.0 statistical software (IBM SPSS Statistics; Armonk, NY, USA). For continuous variables, mean values and standard deviations were calculated. A two-tailed *t* test for continuous and Chi-square test for categorical data was performed. A *p*<0.05 was considered statistically significant.

Results

A total of 146 medical records were available. After the data was thoroughly evaluated, 26 incomplete medical records were excluded and 120 medical records were finally analysed. No statistically significant differences between groups were observed regarding demographic characteristics of patients. The mean age of the population has changed over time, indicating that surgical procedures were performed at an earlier age of the patient in our study population, as shown in Table 1.

Postoperative paracetamol consumption was significantly higher in the NA group (873.5±759.5 mg vs. 625.3±360.9 mg, *p*=0.025), although total paracetamol dose was not different between the groups. A total of 33 children in NA group and 18 in PA group, respectively were given postoperative supplemental analgesics in the recovery room (*p*=0.01; Table 2).

The total weight-adjusted consumption was 47.9±11.4 mg kg⁻¹ in the NA group and 51.1±13.3 mg kg⁻¹ paracetamol in the PA group (*p*=0.164). The total opioid consumption was 5.8±4.7 mg in the NA group and 7.0±4.6 mg morphine equivalents in the PA group (*p*=0.160).

Discussion

This study confirmed that the introduction of pre-emptive analgesia into the standard clinical praxis has no drug-sparing effects in children undergoing elective inguinal herniorrhaphy. Although Hong and co-workers have confirmed that paracetamol was efficient in the terms of fentanyl-sparing effects when combined with ketorolac (8), intravenous paracetamol alone did not reduce the total paracetamol and opioid consumption in our study. The only statistically significant difference introduced after pre-emptive analgesia was the lower number of patients requiring opioid medication in the pre-emptive analgesia group. However, the total opioid consumption and weight-adjusted drug consumption was not decreased with our pre-emptive analgesia regimen as we had expected.

The reasons for our observation may be numerous. Postoperative pain is a multifactorial experience and should be assessed and treated as such. It is the most common sensation experienced by children undergoing invasive procedures but is highly associated with increased anxiety, avoidance, somatic symptoms and increased parental distress. To overcome these issues, managing children undergoing invasive procedures can include numerous strategies, such as use of sedatives, analgesics, anaesthetics or even nonpharmacological methods (9).

Table 1. Demographic characteristic in the two patients groups undergoing elective herniorrhaphy.

	NA group (2011, n=60)	PA group (2013, n=60)	<i>p</i>
Mean age (months)	69.6±49.9	58.7±32.4	0.157
Boys/girls	43/17	44/16	0.841
BMI (kg m ⁻²)	18.3±8.8	16.4±3.7	0.125
Unilateral/bilateral hernia	55/5	52/8	0.558
ASA 1/2/3	52/8/0	46/12/2	0.205
Hospital stay (days)	2.1±0.3	2.0±0.3	0.130
NA: no pre-emptive analgesia; PA: pre-emptive analgesia; BMI: body mass index; data were analysed using <i>t</i> test and Chi-square test.			

Table 2. The analgesic drug consumption in the children undergoing elective herniorrhaphy

Drug	NA group, 2011 year	PA group, 2013 year	p
Sedative premedication (n)	10	8	0.799*
Induction agents			
Sevoflurane via mask (n)	8	5	
Thiopental (n)	25	28	
Propofol (n)	26	26	
Etomidate (n)	1	0	0.603*
Intraoperative opioid*	5.5±4.7	6.0±4.2	0.469
Postoperative opioid	0.3±1.0	0.9±1.6	0.014
Paracetamol pre-emptive dose (mg)	Not given	307.6±192.9	-
Paracetamol intraoperative (mg)	233±167.3	51.4±108.3	<0.001
Paracetamol postoperative (mg)	873.5±759.5	625.3±360.9	0.025
Paracetamol total (mg)	1157.8±908.8	983.0±536.4	0.202
NA: no pre-emptive analgesia; PA: pre-emptive analgesia. *opioid dose calculated as morphine equivalents. Two-tailed t test for continuous and *Chi-square test for categorical data were performed; postoperative paracetamol was calculated as sum of the doses given in the recovery room and surgical ward until patients' discharge.			

The ability to provide safe and effective sedation and analgesia is an important skill. Procedural sedation and analgesia (PSA) is a developing process in the paediatric population, which should allow to maintain sufficient ventilation with preserved protective reflexes in patients. The PSA technique should be an individualised intervention, because pure sedation may be sufficient for imaging studies, while analgesia is required for surgical procedures. The use of propofol has met on some resistance. It seems to be an emerging drug in paediatric emergency; however, other medications, such as ketamine, fentanyl, etomidate and midazolam, have proven their utility and safety over time (10-12).

Opioids have been used for the paediatric pain management for many years, but the high incidence of their side effects (e.g., vomiting, nausea, ileus, biliary spasm and urinary retention) has stimulated a search for analgesics without these unwanted effects. The addition of paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) may decrease opioid requirement (13-15). Michelet et al. (16) in their meta-analysis have shown that perioperative administration of NSAIDs reduces opioid consumption, nausea and vomiting during the postoperative period in children.

A recent study published by Khalili and co-workers has confirmed that pre-emptive paracetamol, administered both in-

travenously and rectally was more effective than was placebo in short-term pain relief after inguinal hernia repair in children (17). The greatest analgesic efficacy of paracetamol was observed during the first 2 h after surgery, and no effects of pre-emptive paracetamol was registered at the fourth, sixth and twelfth postoperative hours between pre-emptive and placebo groups (17). In their study, authors have confirmed the analgesic effect of paracetamol in hernia repair in the paediatric population. They have compared the effects of pre-emptive analgesia vs. no treatment and not the effects of the timing of paracetamol on the overall drug consumption. This issue was stressed in several review articles and meta-analyses, with inconclusive results (18, 19). Møiniche et al. (18) have evaluated studies where the only difference between the study groups was the timing of analgesia and have not found a beneficial effect of pre-emptive analgesia on postoperative pain (19).

After performing a thorough literature review, Dahl and Kehlet (19) concluded that the term 'pre-emptive analgesia' should be disregarded and replaced by the term 'preventive analgesia'. A background for their opinion is the nature of injury-induced central sensitisation, which shares common features during acute and chronic post-surgical pain. Preventive analgesia may influence and reduce the development of persistent postoperative pain (19). Katz et al. (20) shared the same opinion who argued that pre-emptive analgesia must be considered in the broader concept of preventive analgesia. The focus of preventive analgesia is on attenuating the impact of the peripheral nociceptive barrage associated with noxious preoperative, intraoperative and/or postoperative stimuli (20). These stimuli induce peripheral and central sensitisation and increase postoperative pain and analgesic consumption. Preventing sensitisation may reduce pain and analgesic requirements (20). Authors have suggested that preventive analgesia is demonstrated when postoperative pain and/or analgesic use are reduced beyond the duration of action of the target drug, which was defined as 5.5 half-lives of the target drug (20). Until now, there were no studies investigating the effects of preventive paracetamol in the paediatric population and effects of such therapy on the postoperative analgesic requirements.

Perioperative care for children undergoing painful procedures requires careful pain assessment and therapy. In addition, focusing on the pain treatment may result in increased drug consumption, as shown by the results of our study. Although professional skills and knowledge are still determining factors, the goal of perioperative care should be to practice and promote safe sedation and analgesia. The introduction of newer pharmacologic agents and more sensitive pain and anxiety assessment scores may be helpful to achieve this purpose.

The limitation of this study is its retrospective design. It reflects real clinical situations and drug consumption that was the result of an actual pain experience in the hospital setting. Thus,

findings from this clinical observation should focus our attention and future interventions towards possible improvements. Multimodal pain therapy with more active parental involvement may represent such improvement (21). Other drugs, such as sedatives, that were not used in our study population may reduce analgesic, particularly opioid consumption.

Conclusion

Pre-emptive analgesia with paracetamol infusion was proven to be efficient in terms of postoperative pain control but did not reduce the overall analgesic drug administration in children undergoing elective herniorrhaphy. Further studies investigating multimodal perioperative pain treatment using sedatives, nonpharmacological therapies and more active parental involvement in terms of decreased analgesic drugs consumption should be undertaken.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Osijek University Hospital (No. 22512-2/2015).

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

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References

1. Lao OB, Fitzgibbons Jr RJ, Cusick RA. Pediatric inguinal hernias, hydroceles, and undescended testicles. *Surg Clin North Am* 2012; 92: 487-504. [CrossRef]
2. Manoharan S, Samarakody U, Kulkarni M, Blakelock R, Brown S. Evidence-based change of practice in the management of unilateral inguinal hernia. *J Pediatr Surg* 2005; 40: 1163-6. [CrossRef]
3. Available from: http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/ClassificationofChronicPain/Part_III-PainTerms.pdf
4. Kissin I. Preemptive analgesia: problems with assessment of clinical significance. *Methods Mol Biol* 2010; 617: 475-82. [CrossRef]
5. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The Efficacy of Pre-emptive Analgesia for Acute Postoperative Pain Management: A Meta-Analysis. *Anesth Analg* 2005; 100: 757-73. [CrossRef]
6. Wall PD. The prevention of postoperative pain. *Pain* 1988; 33: 289-90. [CrossRef]
7. Brunton L, Chabner B, Knollman B. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 12 ed. New York: McGraw-Hill; 2010.
8. Hong JY, Won Han S, Kim WO, Kil HK. Fentanyl sparing effects of combined ketorolac and paracetamol for outpatient inguinal hernia repair in children. *J Urol* 2010; 183: 1551-5. [CrossRef]
9. American Academy of Pediatrics. Committee on Psychosocial Aspects of Child and Family Health, Task Force on Pain in Infants, Children, and Adolescents. The assessment and management of acute pain in infants, children, and adolescents. *Pediatrics* 2001; 108: 793-7.
10. Meredith JR, O'Keefe KP, Galwankar S. Pediatric procedural sedation and analgesia. *J Emerg Trauma Shock* 2008; 1: 88-96. [CrossRef]
11. Mahajan C, Dash HH. Procedural sedation and analgesia in pediatric patients. *J Pediatr Neurosci* 2014; 9: 1-6. [CrossRef]
12. Dişel NR, Yılmaz HL, Sertdemir Y, Yeşilağaç H, Avci A. Etomidate Versus Ketamine: Effective Use in Emergency Procedural Sedation for Pediatric Orthopedic Injuries. *Pediatr Emerg Care* 2016; 32: 830-4. [CrossRef]
13. Wong I, John-Green StC, Walker SM. Opioid-sparing effects of perioperative paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) in children. *Paediatr Anaesth* 2013; 23: 475-95. [CrossRef]
14. Walker SM. Pain after surgery in children: clinical recommendations. *Curr Opin Anaesthesiol* 2015; 28: 570-6. [CrossRef]
15. Liu C, Ulualp SO. Outcomes of an Alternating Ibuprofen and Paracetamol Regimen for Pain Relief after Tonsillectomy in Children. *Ann Otol Rhinol Laryngol* 2015; 124: 777-81. [CrossRef]
16. Michelet D, Andreu-Gallien J, Bensalah T, Hilly J, Wood C, Nivoche Y, et al. A meta-analysis of the use of nonsteroidal anti-inflammatory drugs for pediatric postoperative pain. *Anesth Analg* 2012; 114: 393-406. [CrossRef]
17. Khalili GR, Shafa A, Yousefi R. Comparison of the effects of pre-emptive intravenous and rectal acetaminophen on pain management after inguinal herniorrhaphy in children: a placebo-controlled study. *Middle East J Anaesthesiol* 2016; 23: 543-8.
18. Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of pre-emptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology* 2002; 96: 725-41. [CrossRef]
19. Dahl JB, Kehlet H. Preventive analgesia. *Curr Opin Anaesthesiol* 2011; 24: 331-8. [CrossRef]
20. Katz J, Clarke H, Seltzer Z. Review article: Preventive analgesia: quo vadimus? *Anesth Analg*. 2011; 113: 1242-53.
21. Stewart DW, Ragg PG, Sheppard S, Chalkiadis GA. The severity and duration of postoperative pain and analgesia requirements in children after tonsillectomy, orchidopexy, or inguinal hernia repair. *Paediatr Anaesth* 2012; 22: 136-43. [CrossRef]