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DIGITALNI AKADEMSKI ARHIVI I REPOZITORIJI

ORIGINAL ARTICLE

More hemodynamic changes in hypertensive versus non-hypertensive patients undergoing breast cancer surgery in general anesthesia - a prospective clinical study

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ABSTRACT

Aim Preoperative comorbidity may significantly influence the conduction of anesthesia and patients' outcome. The aim of this study was to compare a number of anesthetic interventions and the use of non-anesthetic drugs in hypertensive and non-hypertensive patients during general anesthesia for moderately invasive surgery. **Methods** A total number of 88 elective hypertensive (n = 44) and non-hypertensive (n = 44) breast cancer patients were enrolled in the prospective study. Midazolam and infusion of normal saline were given before anesthesia. Etomidate, rocuronium, fentanyl, and sevoflurane up to the 1 MAC were used for the maintenance of anesthesia. Mean arterial pressure (MAP), pulse, core temperature and intraoperative use of all drugs were recorded. MAP was maintained by sevoflurane and infusion replacement. Urapidil and ethylephrine were given if MAP differed > or <30% of baseline, and atropine if heart rate <50 beats min^{-1}. A statistical analysis was made using chi-square and Mann-Whitney tests. **Results** The highest MAP was 133±19.3 in hypertensive and 122±16.5 mmHg in the non-hypertensive patients ($p<0.05$). Hypertensive patients required more anesthetic balancing (42 vs. 23 interventions), more urapidil for intraoperative hypertension (13/44 vs. 2/44, $p< 0.05$) and had more intraoperative hypotensive episodes (23 vs. 12; ns, $p> 0.05$). Intraoperative bradycardia (11/44 vs.7/44) and atropine applications (16 vs. 9, ns, $p> 0.05$) were similar in two groups. **Conclusion** Hypertensive patients required more anesthetic interventions and had higher consumption of vasoactive drugs during anesthesia for breast cancer surgery, suggesting their hemodynamic instability possibly related to the hypertension.

Key words: hypertension, cardiovascular agents, ganglionic blockers, sympatomimetics, anesthesia, general, breast cancer

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INTRODUCTION

Intraoperative hypertension is one of the most common critical events observed during general anesthesia (1, 2). It may be controlled by increase in the inhalation anesthetic concentration or by addition of opioid analgesics and hypnotics (3-5). Hypotension during anesthesia is commonly regulated by volume loading and by decrease in concentration of inhalation anesthetics (6). Such anesthetic maneuvers are efficiently used for blood pressure regulation in the long-lasting surgical procedures. However, in some clinical situations an addition of non-anesthetic drugs will be required for the maintenance of acceptable intraoperative blood pressure values (5).

Despite the large number of reviews describing this issue there are very few original publications in English (3, 4). Hemodynamic changes and use of antihypertensive agents were not compared in hypertensive versus non-hypertensive patients undergoing moderate invasive breast cancer surgery, too. In this type of elective surgery duration of procedure does not far exceed one hour, and quite fast patient turnover is expected (7). Therefore a dose of opioid analgesics should not be excessive to avoid respiratory depression. Instead of anesthetics, other drugs should be preferred for blood pressure manipulations. In the prospective study presented here we have investigated whether these two categories of patients will express differences in the intraoperative blood pressure, pulse and core temperature.

The aim of this study was to compare the hemodynamic oscillations, core temperature and consumption of antihypertensive or sympatomimetic drugs needed for intraoperative blood pressure regulation during general anesthesia for breast cancer surgery in hypertensive and non-hypertensive patients.

PATIENTS AND METHODS

A total number of 130 hypertensive and normotensive breast cancer patients aged 40-76 undergoing radical mastectomy or quadrantectomy with axillary lymph node dissection in general anesthesia were systematically included in the prospective study during a 4-month period. As the number of normotensive breast cancer women was lower, approximate age- matched consecutive patients were evaluated. Patients with renal insufficiency, younger than 40 and older than 76 years were not included in the study. Patients whose tumor was proven as benign after pathohystologic examination were excluded from the study (n=36). Incomplete anesthetic charts were not evaluated (n=6). Finally, two groups of 88 patients were evaluated: normotensive (n=44) and hypertensive (n=44).

A preoperative anesthetic examination was performed one day before the operation. A written informed consent was obtained from all patients. Women were considered as hypertensive if hypertension had been previously recognized and medically treated before the operation. All the patients were treated equally as described below. Anesthetists used for anesthesia were not involved in the data evaluation.

Preoperative ASA (American Society of Anesthesiologists) status, body mass index (BMI), a history of antihypertensive drug use, other comorbid diagnoses and serum values of urea and

Table 1. Preoperative status of women undergoing breast cancer surgery*

Patients' characteristics	Normotensive	Hypertensive
Age	58±10.2	62.1±10.3
Weight	72.2±12.6	79.1±16.5*
Height	165.1±6.8	162.8±7.8
BMI	27.5±7.1	30.0±5,5*
Morbidity (diseases reported)		
Hypertension	0	44
Other cardiovascular†	9	10
Respiratory	0	4
Endocrine	3	12
Gastrointestinal	1	2
Psychiatric	2	5
Other medical	4	3
Other operations	21	30
Chronic drug use (average per patient)	0.4	2.6*
Preoperative urea (mmol l-1)	5.5±1.4	5.7±1.3
Creatinine (mmol l-1)	69.2±14.3	74.0±13.4

*statistically significant differences vs. normotensive patients; †other cardiovascular diseases: arrhythmia, angina pectoris, symptomatic atherosclerosis of major arteries and varicose veins (grade III-IV)

creatinine were recorded in all patients. Two patients in the hypertensive group taking antihypertensive drugs only 1 or 2 times per week (whose highest BP had not exceeded 140-145 mmHg) were given the ASA 1 status. Intraoperative values of mean arterial pressure (MAP) and pulse were recorded noninvasively in five minute intervals (anesthetic machine Primus with the monitor Infinity Delta, Draeger, Germany).

An oral food and liquid intake ceased after midnight. At least 30 minutes before surgery an intravenous line was placed and infusion of normal saline 3 mL kg^{-1} h^{-1} was started. Midazolam (Dormicum, Roche, Netherlands) 0.03 mg kg^{-1} intravenously (iv.) was given 30 minutes before anesthesia. Loading dose of fentanyl (Fentanyl, Janssen, Belgium) 5 μg kg^{-1}, etomidate (Hypnomidate, Janssen, Belgium, EU) 0.2 mg kg^{-1}, rocuronium (Esmeron, Organon, United Kingdom) 0.6 mg kg^{-1} and adjusted doses of inhalation anesthetic sevoflurane (Sevorane, Abbott, Illinois, U.S.A) in the anesthetic gas mixture of O_2:N_2O 35:60 vol% were used for anesthesia. Sevoflurane was used up to concentrations of 1.1 vol% (1 MAC in O_2:N_2O). MAP differing by ≤ 30% of the patient's normal values was maintained by adjustment of sevoflurane concentration or infusion replacement.

Intraoperative hypertension was defined as MAP of ≥ 111 mmHg. Cardiovascular agents used for blood pressure regulation were urapidil, etilefrine and ephedrine. These drugs were given if blood pressure failed to respond to anesthetics, i.e. MAP was >30% of preoperative values despite anesthetic balancing. Atropine was used for intraoperative correction of bradycardia (heart rate <50 beats min^{-1}). A core temperature was measured by temperature probe placed in the hypopharynx after endotracheal intubation and at the end of the surgery.

Statistical analyses were performed with Statistica 6.0 (StatSoft, Inc) for Windows package. All numeric values were expressed as means ± standard deviation. A normality of distribution was analyzed using Kolmogorov-Smirnov test. The statistical analysis was made using Mann-Whitney test for demographic data, laboratory values and hemodynamic parameters. A comparison of frequencies for other data was analyzed by Chi-square test. The level of significance was 5% ($p<0.05$).

RESULTS

Normotensive women in this study were in average four years younger than the hypertensive ones. Hypertensive women showed significantly higher values of body weight and BMI than the normotensive group ($p>0.05$) and had more other comorbidities (Table 1). The most prominent were differences in the incidence of endocrine diseases: diabetes and thyroid diseases needing substitution therapy which were registered in 3 patients (6.8%) in the normotensive group, and in 12 (27.2%) in hypertensive group ($p<0.05$). Cardiovascular, respiratory, gastrointestinal and psychiatric diseases were more common in hypertensive group and reflected in higher ASA status (Figure 1). Preoperative values of urea and creatinine were similar in normotensive and hypertensive patients. An analysis on the drug use revealed that all hypertensive patients took in average 2.6 drugs, whereas 37% of normotensive patients used one drug ($p<0.05$). Only one normotensive patient routinely takes 2 drugs. Previous operations were reported in 47% of patients in normotensive and 68.2% in hypertensive group (Table1).

Intraoperative values of minimal MAP measured were not significantly different between two study groups. However, intraoperative MAP

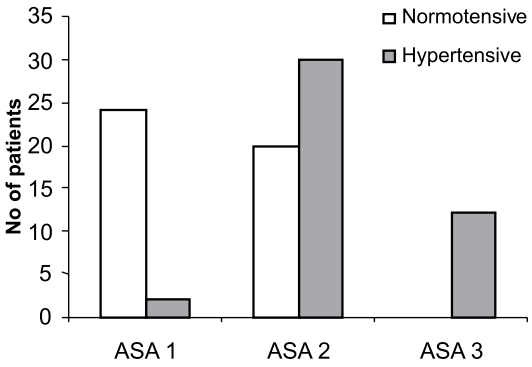

Figure 1. ASA (American Society of Anesthesiologists) physical status in the normotensive and hypertensive group.

pressure requiring manipulation upwards was observed in 12/44 vs. 23/44 normotensive and hypertensive women ($p< 0.05$) (Table 2). In the majority of patients it was registered after the anesthetic induction and during an operative field washing, and was managed by infusion replacement or reduction of the sevoflurane concentration. Only one hypertensive breast cancer patient needed epinephrine injection due to hypotension.

Eleven patients in the normotensive and 3 in the hypertensive group had no episode of intraoperative hypertension ($p<0.5$). The highest MAP measured in each patient was significantly higher in the hypertensive than in the normotensive group ($p<0.05$). A difference between two extreme MAPs was 42±16.5 and 54±12 mmHg in the normotensive and hypertensive group. In the hypertensive group 11/44 patients and only one in the normotensive group needed urapidil for intraoperative blood pressure control ($p< 0.05$).

After all anesthetic and nonanesthetic drug interventions for treatment of both hypotension and hypertension were registered in 12/44 patients in the normotensive and only 5/44 in the hypertensive group were considered as circulatory stable, requiring no blood pressure manipulations ($p<0.05$).

The highest registered values of pulse observed in both groups did not differ. Intraoperative tachycardia needing manipulation down was registered in 3 normotensive and in only 1 hypertensive patient. Such differences can be explained by a significant blockade of myocardial conductivity in hypertensive patients taking drugs (Table 2).

Table 2. Parameters observed during anesthesia in normotensive and hypertensive women undergoing breast cancer surgery*

Group	Normotensive (n=44)	Hypertensive (n=44)
Pulse values: Maximal observed	89.1±16.2	89.2±14.7
Minimal observed	59.5±12.4	56.6±7.9
Bradycardia (No patients)	7	11
Atropine (applications)	9	16
MAP* values: Maximal	122±16.5	133.2±19.3†
Minimal	79.8±11.4	80.8±13.2
Drugs used for BP correction (No of patients)	2	13
Core temperature decline (°C h-1)	0.36±0.27	0.40±0.25
Duration of surgery (minutes)	62,6±20.9	63,7±24,4
Infusion dose (mL)	877± 440	837± 590

*MAP, mean arterial pressure, BP blood pressure;
†$p < 0.05$ vs. normotensive patients

Intraoperative bradycardia was observed in the similar number of patients in both groups. Tachycardia and significant increase in MAP, which cannot be balanced by anesthetics, were observed in 1 patient in both groups and efficiently decreased by verapamil. The use of atropine and antiarrhythmic drugs was similar in two groups.

In all patients acceptable values of blood pressure and pulse were achieved by drugs used.

A decline in core temperature was higher in the hypertensive group, although not statistically significant. Mean duration of surgery did not differ between groups. A higher amount of infusions was given in the non-hypertensive group, although those differences were not significant (Table 2).

DISCUSSION

This study demonstrated more cardiovascular instabilities in hypertensive patients in comparison with normotensive. Hypertensive surgical patients needed more anesthetic balancing and more nonanasthetic drugs for intraoperative blood pressure regulation, mostly for blood pressure manipulation down.

Hypertension is one of the most common diseases observed in Croatian and other populations

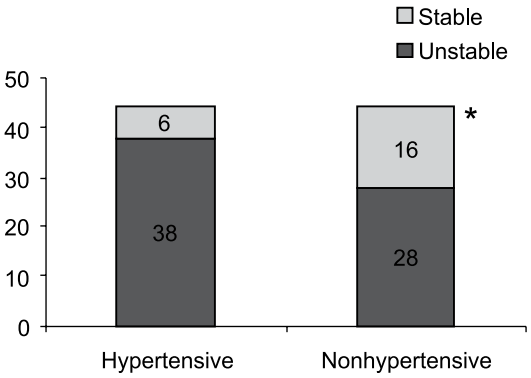

Figure 2. Haemodynamic instability in breast cancer patients: MAP (mean arterial pressure) > or < 30% from baseline

in this area (4, 8, 9). In the population older than 18 Panagiotakos observed incidence of hypertension of approximately 30%, which was mostly untreated (9). It is likely that some of our patients who were not declared as hypertensive have uncontrolled disease, too.

The incidence of hypertension is higher in older, postmenopausal women (10-12). It was thus registered in the majority of breast cancer women. This fact has become one of limitations in this study, rendering a difficult study inclusion. In the primary study design patients were assumed to be age-matched if the age difference was not more than ±2 years. However, after the first patients were enrolled it became apparent that the majority of patients requiring breast cancer surgery were hypertensive. Non-hypertensive breast cancer women were in average 10 years younger so that older normotensive controls were lacking, whereas older hypertensive women were not included. This resulted in a lower number of patients involved in the study.

Hypertension is a major risk factor for several cardiovascular diseases and diabetes (8). Moreover, it is associated with higher BMI than in normotensive population, as observed in this study (Table 1) (9). A result is a poorer physical status of hypertensive patients.

Intraoperative hypertension is one of the most common incidents reported during anesthesia (1). It may be precipitated by insufficient analgesia and by excessive surgical stimulation. In moderate invasive breast cancer surgery, sympathetic and painful stimulations are not intense. This type of surgery itself requires neither the use of high dose opioids nor antihypertensive agents. Until now particular differences towards intraoperative blood pressure values expressed by hypertensive and normotensive women during breast cancer surgery were not described. This may result in the opinion that complications are rare in breast cancer surgery and mostly dependent on associated diseases (13). In this study we made an effort to measure whether population characteristics, i.e. presence of hypertension itself will reflect in more hemodynamic oscillations. Values of MAP and not systolic blood pressure were recorded since MAP reflects more accurately real systemic perfusion rather than systolic pressure.

Untreated intraoperative hypotension or hypertension may lead to impaired organ perfusion and permanent damage, particularly in patients with compromised cardiovascular function. The hypotension was commonly associated with heart rate and rhythm abnormalities (1, 6). This study revealed more interventions needed for intraoperative maintenance of pulse and blood pressure in the majority of hypertensive patients. Although maximal values of MAP were higher in hypertensive group, these patients expressed more episodes of hypotension after the induction and during maintenance phases. Intraoperative hypotension in the hypertensive group may be influenced by antihypertensive drugs used by every particular patient.

After the surgical incision the hypertensive patients expressed more pronounced increase in the MAP. Higher MAP values were observed in the similar number of blood pressure measurements in both groups, but were usually well controlled by anesthetic maneuvers in the non-hypertensive group. Such management proved to be insufficient, and more urapidil injections were needed for blood pressure regulation during intraoperative blood pressure management of hypertensive patients. Urapidil efficiently controlled all intraoperative hypertensive episodes, as observed in the recent literature findings (14). Although some authors use beta blockers, we have chosen urapidil to avoid bradycardia (15).

A hypothesis that hypertensive patients have increased sympathetic drive which should be reflected by minor decline in the core temperature was not proven in this study. A more pronounced but statistically insignificant heat loss was observed in hypertensive patients. This result differed from others who reported lower temperature decrease and hypertensive patients (16). It may be influenced by obesity and diabetic peripheral neuropathy which delays the onset of thermoregulatory vasoconstriction (17). Such decrease should have higher impact on intraopera-

tive care during more aggressive and long-lasting surgery.

Hemodynamic instability demands a specific approach to hypertensive patients by means of maintaining the blood pressure under control so that it could not cause harm to patient. Higher standards of monitoring have to be applied during the intraoperative management of hypertensive patients. Closed loop systems may be useful in many instable hypertensive individuals (18). There are several maneuvers that could reduce intensity of blood pressure oscillations. Intense cardiovascular oscillations may be decreased by preoperative antihypertensive drug intake on the morning of surgery. This clinical approach was not applied in this study, since we have personally made observations noting that patients taking antihypertensive drugs on the day of the surgery had more intraoperative hypotensive episodes, especially if were given sedative premedication. Adequate preoperative hydration may reduce episodes of intraoperative hypotension. The doses of drugs used for premedication, induction and intraoperative blood pressure management should be balanced against the resulting clinical situation. Preoperative small dose of fentanyl is a common practice, and was used for patients included in our study (19).

A direct consequence of frequent cardiovascular oscillations is an increase in the consumption of anesthetic and nonanasthetic agents together with higher equipment and personnel engagement. Those may result in the increased cost of anesthesia in the hypertensive patients. In the study of *Tartter et al.* the history of a heart disease, hypertension, diabetes, obesity, and ASA status were significantly associated with prolonged hospital stay after breast cancer surgery (13). An increased consumption of drugs similar to our results was observed in ambulatory non-surgical hypertensive patients (8). A detailed cost analysis of hospital treatment of hypertensive patients undergoing breast cancer surgery was not a goal of this study. It should be evaluated by Health Insurance officers, since operative treatment of hypertensive patients appears to be more expensive than of normotensive patients.

The issue of whether more frequent and intensive hemodynamic oscillations in hypertensive patients have an impact on postoperative recovery and long term surgical and medical outcome should be a subject of a new clinical study.

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