Myocardial Protection with Sevoflurane in Patients with Cardiac Risk Undergoing Non-cardiac Surgery

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Objective: Evaluation of cardioprotective effects of sevoflurane compared with propofol in high-risk cardiac patients undergoing non-cardiac surgery.
Material and methods: Prospective study enrolling 14 patients with cardiac risk Lee's score > 3 points, undergoing abdominal elective surgery. The patients were divided into two groups: Group S (sevoflurane) – 8 patients who received balanced anesthesia with sevoflurane; Group P (propofol) – 6 patients receiving total intravenous anesthesia - target control infusion (TIVA-TCI). All patients were monitored hemodynamically, cardiac biomarkers (troponine I – TnI, the precursor of brain natriuretic peptide – proBNP, myocardial creatine kinase – CKMB) and inflammatory tests (high sensitive C-reactive protein – CRP, fibrinogen – FBG, interleukin 6 – IL6) were registered perioperatively.
Results: All patients had a decrease of mean arterial pressure (MAP) after induction, with significant values in Group P (48.4±3.82 mmHg). There were no acute cardiac perioperative events and the concentration of TnI after surgery was significantly lower in patients with sevoflurane anesthesia (0.017±0.01 ng/ml vs. 0.2±0.18 ng/ml) at 12 h and 24 h respectively ($p < 0.05$). CKMB had lower postoperative values in Group S vs. Group P. ProBNP was elevated preoperatively in all patients and it is correlated with increased cardiac risk. In postoperative period the patients have lower levels in Group S compared with Group P ($p < 0.05$). IL6 showed a significant decrease in patients in Group P at 12–48 h after surgery.
Conclusion: Anesthesia with sevoflurane, in patients with increased cardiac risk undergoing non-cardiac surgery, was accompanied by decreased values of TnI, proBNP and CKMB postoperatively, compared with propofol anesthesia.

Keywords: cardiac risk, sevoflurane, cardioprotection, non-cardiac surgery

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Introduction

Perioperative myocardial ischemia is a common complication that increases mortality and morbidity after cardiac and non-cardiac surgery. Patients with coronary artery disease or coronary risk factors, undergoing non-cardiac surgery, show an incidence of perioperative myocardial ischemia between 18–74 % [1]. To prevent and reduce perioperative myocardial ischemia, some therapeutic approaches have been proposed for improving the relationship between demand and supply of oxygen to the myocardium [1,2,3].

In recent years, it was shown that in patients with cardiovascular risk, some anesthetics used for the induction and maintenance of general anesthesia, such as volatile anesthetics, intravenous anesthetics and opioids, have a protective effect on ischemia-reperfusion injury, independent of hemodynamic effects [4,5,6,7].

In 2002, the American College of Cardiology and American Heart Association (ACC/AHA) published their Guidelines for preoperative cardiovascular assessment in non-cardiac surgery. These Guidelines were updated in 2007 [8], and they recommend the use of general anesthesia with sevoflurane in patients with cardiac risk undergoing non-cardiac surgery (recommandation II B).

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The aim of the present study is to compare the cardioprotective effects of sevoflurane with those of propofol, in patients with increased cardiac risk, undergoing major abdominal surgery.

The main objective is to assess hemodynamic status, cardiac and inflammatory markers of patients undergoing non-cardiac surgery in the perioperative period, with general anesthesia balanced with sevoflurane (AG) vs. total intravenous general anesthesia - target control infusion with propofol (TIVA-TCI).

Materials and methods

Following the agreement of the Ethics Committee of the ELIAS Emergency University Hospital, Bucharest and after written consent obtained from each patient, we conducted a prospective clinical study, enrolling all patients with increased cardiac risk (Lee's score > 3 points, MET ≤ 4), over 18 years old, undergoing elective major abdominal surgery.

Excluded from the study were patients with recent acute myocardial infarction (less than 6 weeks), those undergoing myocardial revascularization procedures and those with recent stroke (within 3 months).

In order to assess myocardial protection we used the following evaluation methods: transthoracic echocardiography to assess left ventricular diastolic function, global and segmental ejection fraction (EF), 12-derivation elec-

trocardiogram (ECG) (ST segment, Q necrosis wave presence), serum levels of cardiac biomarkers and enzymes: creatine kinase MB (CKMB), troponine I (TnI), precursor of brain natriuretic peptide (proBNP), aspartate transaminase (AST) and alanine transaminase (ALT). We also followed the acute inflammatory tests: fibrinogen (FBG), high sensitive C-reactive protein (CRP) and interleukin 6 (IL6).

Patients with a mean age of 73.14±9.04 years were randomly divided into two groups depending on the type of general anesthesia, as follows: Group S (n=8) – sevoflurane anesthesia (AG) and Group P (n=6) – propofol anesthesia (TIVA-TCI).

During the preanesthetic assessment we established the following: preoperative anesthetic risk (ASA scale), cardiac risk based on Lee's score, functional capacity estimation MET and cardiovascular risk factors identification. After enrolling the patients in the study, we performed: ECG, transthoracic echocardiography, common biologic tests, hemoglobin, urea, creatinine, cholesterol, glycemia, coagulation tests, inflammatory tests (FBG, ALB, CRP, IL6), cardiac enzymes (CK, CKMB, CKMB/CK, AST, ALT) and biomarkers (TnI, proBNP). The ACC/AHA Guidelines recommendations were used in terms of cardiac drug therapy.

Preoperative thromboprophylaxis (enoxaparin s.c.) was performed 12 h before surgery. The premedication was performed with alprazolam 0.5 mg per os (p.o.), the night before surgery.

Preoperatively, for all patients, a peripheral venous catheter was placed, an arterial catheter in the radial artery and thoracic epidural catheter (T5–T9) depending on the type of abdominal surgery. All patients received general anesthesia combined with epidural analgesia with ropivacaine 0.5%.

Intraoperative monitoring was carried out according to the standard procedure: ECG with 5 derivations, ST segment monitoring, peripheral O2 saturation (SpO_2), anesthesia depth assessment with the bispectral index (BIS = 40–50), neuromuscular blockade assessment, central/peripheral temperature, respiratory parameters and diuresis.

Invasive hemodynamic monitoring was performed before induction of anesthesia, with FloTrac sensor and Vigileo monitor (Edwards Lifesciences) system, measuring: invasive mean arterial pressure (MAP), cardiac flow (CF), cardiac index (CI), systemic vascular resistance (SVR), stroke volume variation (SVV), and tissue oxygen supply (DO_2). Central venous O_2 saturation at the jugular level ($ScvO_2$) and central venous pressure (CVP) were monitored by a PreSep central venous catheter, with optical-fibre and Vigileo monitor (Eduards Lifesciences), mounted after induction of general anesthesia.

The anesthetic technique in the sevoflurane group consisted of premedication with midazolam 0.02 mg/kg administered intravenously (i.v.) and induction performed with fentanyl 2 μg/kg, rocuronium 0.6 mg/kg and thiophental 3–5 mg/kg. Maintenance of anesthesia was carried out with sevoflurane (MAC 1.8–2.2) into oxygen and air mixture 2/3, rocuronium 0.3 mg/kg (i.v.) to the ratio of T1/T3 >25 % and fentanyl 0.1 μg/kg at 20–40 min.

The anesthetic technique in the propofol group was TIVA-TCI, premedication with midazolam in the same dose, induction with propofol 4–6 μg/ml plasmatic concentration, Marshal model built-in to TCI pump (Braun) and remifentanyl 2–4 ng/ml plasmatic concentration, Minto model built-in to TCI pump, followed by administration of rocuronium 0.6 mg/kg. Maintenance was achieved with propofol 4–8 μg/ml, remifentanyl 2–4 ng/ml, rocuronium 0.3 mg/kg.

In 10–20 min following the intubation, ropivacaine 0.5% (8–12 ml) was injected into the epidural catheter. Local anesthetic was repeated at 2–2.5 h, in the same concentration, if surgery lasted more than 3 h.

Intraoperative fluid intake was 15 ml/kg/h, supplemented with the estimated and measured hourly losses. Blood transfusion was performed at hemoglobin levels below 9.5 g/dl. We registered all the intraoperative cardiac events, the need for vasopressor (ephedrine) or positive inotropic drug administration and any events related to the surgical act. Awakening was allowed in the operating room.

Ropivacaine was administered on the epidural catheter at the end of the intervention, in analgesic concentration (0.25%). Transfer to the postoperative care unit was made at an Aldrett score > 8 points. Postoperative analgesia was multimodal – epidural analgesia combined with NSAIDs.

Patients from both groups were monitored with standard and invasive methods for 48 h. Serial hemodynamic measurements were performed, cardiac enzymes, cardiac biomarkers and inflammatory tests were carried out immediately after induction (T1), and in the postoperative period at 1 h (T2), 12 h (T3), 24 h (T4) and 48 h (T5). We registered all occurring perioperative cardiac events. Transthoracic echocardiography was performed at 24 h and 48 h.

Data were stored electronically and analyzed using the EPI INFO 2002 program. Data comparison between the two groups was performed using the Student's t-test for paired samples. A p value of <0.05 was considered to be statistically significant.

Results

The studied groups showed no significant differences regarding demographic data (age, weight, height), anesthetic risk (ASA), cardiac risk (Lee's score), chronic cardiac drug therapy, associated diseases, duration of anesthesia and type of surgery (abdominal surgery).

There were no significant differences regarding preoperative hemodynamic parameters (MAP, HR, CI, and $ScvO_2$) between the two groups. There was a MAP decrease after induction in all patients, being statistically significant in Group P (48.4±3.82 mmHg, $p<0.05$). This can be explained by the important vasodilation produced by the administration of propofol in induction and demon-

Table I. Patient characteristics. Mean values (SD = standard deviation) and absolute numerical values.

Patient characteristics	Group P (n=6)	Group S (n=8)	p value
Age, y	80±5.19	68±7.95	ns
Weight, kg	77±12.5	75±11.1	ns
Height, cm	168±4.4	167±7.3	ns
BMI, kg/m^2	26.9±3.1	25.4±2.2	ns
Diabetes, n	4	3	0.28
Hypertension, n	3	8	0.02
Chronic renal dysfunction, n	2	1	0.34
Dyslipidemia, n	2	4	0.53
Peripheral vasculopathy, n	1	2	0.70
Previous myocardial infarction, n	2	3	0.87
Previous coronary artery bypass graft, n	0	1	0.36
Coronary artery disease, n	5	8	0.02
Smoker, n	4	5	0.87
NYHA total, n	3	5	0.63
NYHA Class II, n	2	4	0.53
NYHA Class III, n	1	1	0.82
Ejection fraction, %	52±8	50±10	0.68
Medication			
Beta-blockers, n	2	6	0.11
Calcium channel blockers, n	1	2	0.70
ACE inhibitors, n	6	8	0.02
Statins, n	3	4	0.98
Antiaggregants, n	6	8	0.02
Digoxin, n	1	1	0.82
Oral antidiabetics, n	4	3	0.28
Furosemide, n	1	3	0.39
Spironolactone, n	1	1	0.82
Type of surgery			
Right hemicolectomy	3	2	0.33
Left hemicolectomy	1	1	0.82
Total gastrectomy	1	2	0.70
Subtotal gastrectomy	1	2	0.70
Duodenopancreatectomy	0	1	0.36
Time of the anesthesia, h	3.84±1.61	4.12±0.92	0.52
ASA Class:			
II, n	2	5	0.28
III, n	4	3	0.28
Time in ICU, hours	48.25±3.65	41.85±6.81	0.67
Deaths in 30 days, n	1	0	0.98

BMI = Body Mass Index
NYHA Class = New York Heart Association Functional Classification
ACE = Angiotensin Converting Enzyme
ASA Class = American Society of Anesthesiologists risk classification system
ICU = Intensive Care Unit
ns = not significant

p < 0.05 is statistically significant

strated by the increase of SVR in Group P (T1, 1283.48± 436.52 dyne•sec/cm^5).

Also, 3 patients from Group P and 1 patient from Group S had an important decrease in blood pressure (hypotension – hMAP), requiring the administration of a vasopressor (ephedrine, 5–10 mg).

Although the average duration of anesthesia was 4 hrs, no events were noticed and it was not necessary to administer positive inotrop medication in any patient. In terms of hemodynamic postoperative parameters (CO, CI, $ScvO_2$ and DO_2), there were no significant differences between the two groups.

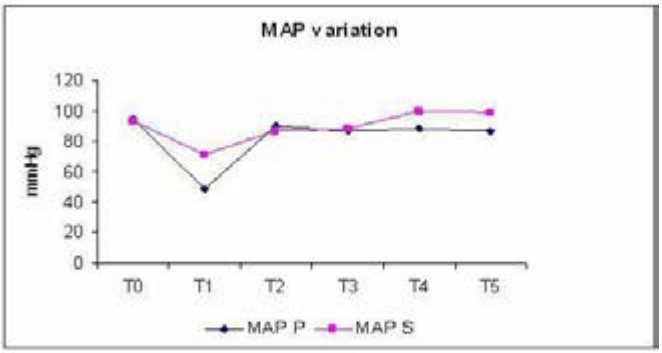

Fig 1 – Change in MAP for the propofol(n=6) and sevoflurane(n=8) from before anesthesia (T0), after intubation(T1), at 1 hour(T2), 12hours(T3), 24hours(T4), 48 hours(T5) postoperatively.

Fig. 1. Mean arterial pressure variation

Intraoperatively, 3 patients from Group S and 2 patients from Group P required autologous blood transfusion to maintain the hemoglobin level (Hb) over 9.5 g/dl.

No acute cardiac events were recorded in the postoperative period (with the exception of some episodes of hypertension – HMAP in 2 patients from Group P and 1 patient from Group S, 1 h after surgery). Also, 1 patient from Group S showed an episode of atrial fibrillation postoperatively, at 24 h, and continuous infusion of amiodarone was administered. This episode was explained by the decrease of Hb from 9.7 g/dl to 7.6 g/dl, as a result of an increase in abdominal drainage. It is to be noted that this patient had the longest surgery (6 h) and required both intraoperative and postoperative blood transfusion immediately after surgery.

In the postoperative period, there were no significant differences in the levels of cardiac enzymes (AST, ALT) in all patients, but instead significantly lower CKMB levels were found in Group S at 1 h after surgery (11.75±7.41 U/l vs. 39.33±52.62 U/l, p <0.05) and up to 48 h after surgery (12.25±6.23 U/l vs. 37.3±55.15 U/l, p=0.039).

Note that in patients with sevoflurane anesthesia we found a significantly lower concentration of TnI (0.017±0.015 ng/ml vs. 0.2±0.18 ng/ml) at 12 h and 24 h respectively (p=0.036). TnI did not show significant differences between groups at 48 h postoperatively.

Instead, proBNP was elevated before surgery in all the patients (405±264.7 pg/ml), being correlated with an increased cardiac risk Lee' score > 3 points (p=0.005). It was also found that proBNP value was significantly lower in

Table II. Cardiac and hemodynamic perioperative events. Absolute numerical values.

Perioperative events	Group P (n=6)	Group S (n=8)	p value
hMAP postinduction, n	3	1	0.12
Vasopressor administration, n	3	1	0.12
HMAP postoperative, n	2	1	0.34
AF, n	0	1	

hMAP = Hypotension
HMAP = Hypertension
AF = Atrial fibrillation

p < 0.05 is statistically significant

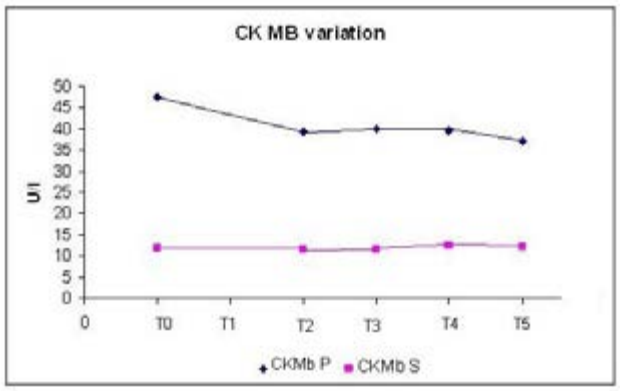

Fig 2 – Change CKMB for the propofol(n=6) and sevoflurane(n=8) from before anesthesia (T0), after intubation(T1), at 1 hour(T2), 12hours(T3), 24hours(T4), 48 hours(T5) postoperatively

Fig. 2. Creatine Kinase MB variation

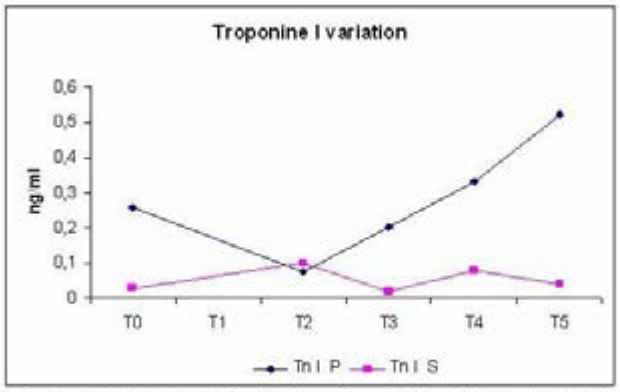

Fig. 3 – Change Tn I for the propofol(n=6) and sevoflurane(n=8) from before anesthesia (T0), after intubation(T1), at 1 hour(T2), 12hours(T3), 24hours(T4), 48 hours(T5) postoperatively

Fig. 3. Troponine I variation

Group S compared to Group P at 1 h (446.17±159.24 pg/ml vs. 1398.83±819.4 pg/ml), and 12 h postoperatively (854.62±427.51 pg/ml vs. 1192.16±822.92 pg/ml, p=0.040), respectively. Subsequently, patients in both groups recorded similar levels of this biomarker.

CRP inflammatory test showed no significant changes between groups. In opposition, IL6 showed a significant increase postoperatively compared to preoperative values in both groups, but at 48 h its values came closer to the preoperative ones (Group P, 49.31±13.47 pg/ml vs. 51.63±37.5 pg/ml). The IL6 level in Group S maintained a high value even at 48 h (162.18±249.43 pg/ml). Albumin and fibrinogen showed no significant variations between the two groups.

Admission period in the intensive care unit was similar between the two groups, with an average of 48.25±3.65 h in Group P and 41.85±6.81 h for Group S.

In the first 30 days after surgery there was only 1 death in Group P, due to surgical causes (digestive leakage). There were no deaths of cardiac causes in this period.

Discussion

Myocardial protection induced by some anesthetics, has been explained by numerous experimental studies as a result of a preconditioning-type phenomenon [2,3]. In the literature there are few data on the cardioprotective effect of anesthetics in non-cardiac surgery [1,6].

Our study compared the myocardial protective effects of sevoflurane and propofol in patients with major cardiac risk undergoing non-cardiac surgery, monitoring the evolution of hemodynamic parameters, cardiac enzymes and cardiac biomarkers of these patients.

Elevated levels of preoperative proBNP (over 180 pg/ml) correlates with major cardiac risk for patients in the study and indicates the risk of postoperative cardiac complications in these patients [4,10,11].

Although MAP values were similar in all patients preoperatively, it was found that after induction of general anesthesia in patients with TIVA-TCI, IMAP presented a significant decrease due to vasodilatation produced by propofol, without being accompanied by changes in cardiac index.

No acute cardiac events were recorded postoperatively, but episodes of hypertension were instead present in both groups without any consequence on cardiac function. Hemodynamic changes were comparable between the two groups, which can be confirmed by literature data showing that propofol also has cardioprotective effects, but they are less known and studied than those of volatile anesthetics [12,13].

However, Yildirim et al. found a significant improvement of cardiac function in patients who received anesthesia with sevoflurane, compared with those who received propofol. In addition, plasma levels of TnI (but not of CKMB) were significantly decreased in the group that received sevoflurane [4]. These data are inconsistent with the data obtained by us, which showed a significant decrease of TnI in Group S in the first 24 h postoperatively, but also of CKMB values in the same patients.

Recent studies showed that high CRP correlates with acute cardiac events [14,15]. These studies have shown that its value reaches maximum in the 3rd day, returning to normal after 2 weeks [15].

In our study, although CRP had higher values during the first 24 h postoperatively, it decreased significantly after 48 h, especially in Group S, recording lower values than

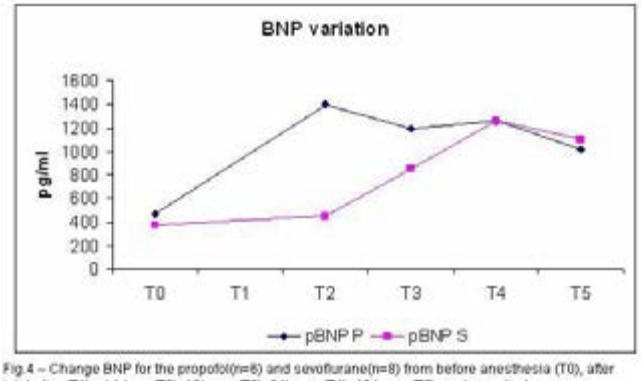

Fig.4 – Change BNP for the propofol(n=6) and sevoflurane(n=8) from before anesthesia (T0), after intubation(T1), at 1 hour(T2), 12hours(T3), 24hours(T4), 48 hours(T5) postoperatively

Fig. 4. Precursor of brain natriuretic peptide variation

the average established in literature for high-risk cardiac patients undergoing surgery.

Data from the literature confirm that the release of IL6 is lower in patients undergoing anesthesia with propofol versus inhalation anesthesia, as a result of the suppression of the inflammatory response by TIVA anesthesia [14].

Although our study showed an increase of IL6 at 1 h postoperatively in Group P, subsequently the values of this marker of inflammation were lower in the propofol group compared to the sevoflurane group.

New data obtained in this study presents differences with data from the medical literature (low incidence of postoperative cardiac events), which can be explained by the fact that the study has some limitations (the small number of patients limit the statistical power). We mention that the study is underway to include a larger number of patients, with plans to evaluate patients at 1 month, 6 and 12 months postoperatively.

Conclusions

Sevoflurane anesthesia in patients with increased cardiac risk in non-cardiac surgery provided a better hemodynamic stability and was accompanied by decreased postoperative concentrations of TnI, CKMB and proBNP levels, compared with TIVA-TCI anesthesia.

Increased value of preoperative proBNP was correlated with increased cardiac risk Lee's score, but not correlated with the incidence of acute cardiac postoperative events.

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