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Comparison of sevoflurane and propofol anaesthetic regimes in respect to the release of troponin I and cystatin C in off-pump myocardial revascularisation: a randomised controlled trial

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ABSTRACT

Objective. Sevoflurane has been used in cardiac surgery because of its protective effects on the myocardium from ischaemic injury. We wanted to test the hypothesis that sevoflurane has beneficial effects on the heart and kidneys in comparison to propofol.

Methods. We conducted a randomised controlled study, with balanced randomization blocked by sex. The participants were 62 patients undergoing off-pump myocardial revascularization (44 men and 18 women), who did not have a myocardial infarction less than 24 hours before the start of the operation and who had normal serum values of troponin I preoperatively. The surgery and the measurements were conducted according to the same protocol for both groups. Propofol was used for the induction of anaesthesia in both groups; anaesthesia was continued with either propofol or sevoflurane. Troponin I and cystatin C plasma concentrations were determined in eight consecutive blood samples, starting before induction of anaesthesia and ending 48 hours after admission to the intensive care unit (ICU). The data were log-transformed and analysed using analysis of variance.
Results. We observed a clear and highly statistically significant effect of time for troponin I ($p<0.001$) without statistically significant differences between the groups (either main or interaction effects). For the majority of patients, the measurements rose quickly upon reperfusion and reached a peak 12 hours after admission to the ICU, descending approximately back to the reperfusion level 48 hours after admission to the ICU. Similar inferences were reached for cystatin C, for which the time-course was approximately bath-shaped.

Conclusion. We observed no clear superiority of either sevoflurane or propofol anaesthetic regime in off-pump myocardial revascularisation.

Key words: anaesthetic regime, cardioprotection, kidney function, heart surgery

INTRODUCTION

Perioperative myocardial ischaemia can increase morbidity and mortality after cardiac surgery. To prevent or lessen myocardial ischaemia during and after surgery, various approaches have been proposed that are directed towards modulation of the myocardial oxygen supply-demand relationship. (1)

The protective mechanism of ischaemic preconditioning might greatly exacerbate the ischaemia symptoms of an already injured heart. (2) With the use of halogenated anaesthetics, anaesthetic preconditioning can be achieved, mimicking the protective role of ischaemic preconditioning and provoking the adaptive responses of the myocardium to ischaemic insult. (3-7)

The protective effect of sevoflurane is most apparent (8-10) when applied throughout coronary artery bypass surgery, with the use of cardiopulmonary bypass (CPB) in a certain minimal alveolar concentration (MAC) range. It has also been reported that the use of sevoflurane in an anaesthetic regime reduces postoperative morbidity and mortality. (11)

Acute kidney injury is a major perioperative complication after cardiac surgery, which is associated with significant morbidity, mortality and related costs. (12) After sevoflurane preconditioning, postoperative kidney function can be preserved in patients undergoing coronary artery bypass graft surgery under CPB, as demonstrated by a lower serum cystatin C level. (13)

Based on the findings summarised above, we conducted a study testing the hypothesis that sevoflurane protects the heart and the kidneys in comparison to propofol in off-pump heart surgery. Cardioprotection was assessed during and after the operation by the release of troponin I, the biochemical marker of myocardial ischemia. Kidney function was monitored via cystatin C serum levels at the same time-points as troponin I levels.

METHODS

Patients

The study was registered with the Health Insurance Institute of Slovenia (registration no. 20100301, principal investigator Nina Kosmač, date of registration 5th November, 2009, trial duration 2010-2012). The national legislation and local research practice guidelines did not require or recommend international registration at the time of study design, registration and ethical approval. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (http://www.kme-nmec.si/) on 31 December 2009 (research no. 95/11/09) as a continuation of previously approved research (no. 82/05/04 and 92/01/06). All patients gave informed consent, were aged 18 years or older, and had ischaemic heart disease without valvular disease.

We conducted a randomised clinical trial. It was performed prospectively in patients scheduled for off-pump heart surgery. None of the patients had myocardial infarction less than 24 hours before the start of surgery and all patients had normal serum values of troponin I preoperatively.

Balanced computerised randomisation was employed, which involved 62 patients (44 men and 18 women), so that there were 31 patients in each group. Because randomisation was blocked by sex, there were 22 men and 9 women in each group. The patient recruitment process is summarised in figure 1.

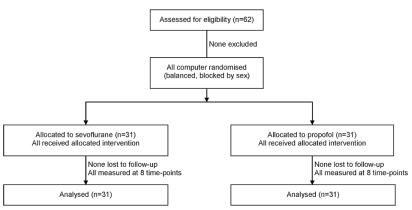

Figure 1. Flow-chart of patient recruitment.

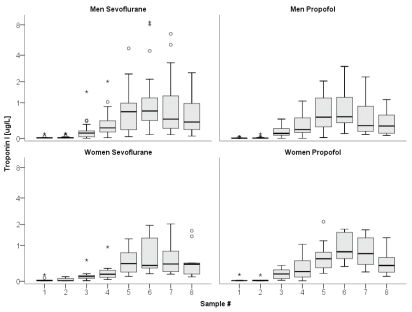

Figure 2. Distributions of troponin I measurements.

Notes: vertical axis is in logarithmic scale in order to show the variables as they were entered into the ANOVA models; boxplots: thick line – median; box – interquartile range; whiskers – non-outlier range; circles – outliers; asterisks – extremes.

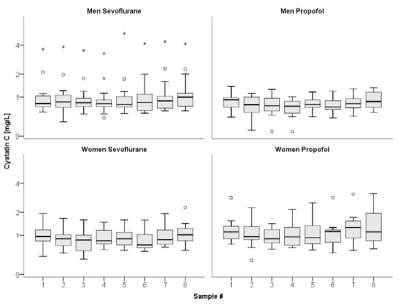

Figure 3. Distributions of cystatin C measurements.

Notes: vertical axis is in logarithmic scale in order to show the variables as they were entered into the ANOVA models; boxplots: thick line – median; box – interquartile range; whiskers – non-outlier range; circles – outliers; asterisks – extremes.

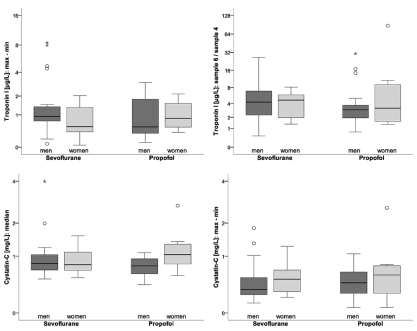

Figure 4. Distributions of the calculated parameters summarising the time-course of the measurements.

Notes: vertical axis is in logarithmic scale in order to show the variables as they were entered into the ANOVA models; boxplots: thick line – median; box – interquartile range; whiskers – non-outlier range; circles – outliers; asterisks – extremes.

Anaesthesia and surgical procedure

Anaesthesia and surgery were conducted similarly in both groups except for the maintenance of general anaesthesia. All preoperative heart medications were continued until the morning of the surgery, with the exception of angiotensin-converting-enzyme inhibitors. All patients fasted from midnight. Bromazepam 1.5-3.0 mg was given to patients on the evening before the operation and in the morning on the day of the operation, unless the patient had already been taking alprazolam at home; in the latter case, 0.5 mg alprazolam was given in the evening and 0.25 mg in the morning. In addition, a proton-pump inhibitor (pantoprazole or omeprazole) was administered in the morning before the operation. After premedication on the ward, the patients were admitted to the anaesthetic room. A peripheral venous line was inserted and an arterial line was placed in the radial artery..

Propofol was used for induction of anaesthesia by continuous infusion of 10 mg/kg body weight (BW)/h, which was changed to 3-5 mg/kg BW/h after 2 minutes, after which midazolam (1 to 2 mg) and fentanyl (by boluses of 5 to 7 μg/kg BW) were added. Vecuronium 0.1 mg/kg BW was used for muscular relaxation in all patients. Patients were intubated and mechanically ventilated with oxygen-air mixture (FiO2 0.4). In the sevoflurane group, the infusion of propofol was stopped after intubation, and anaesthesia was maintained with sevoflurane 1 to 1.5 MAC. In the propofol group, we continued with an infusion of propofol 3-5 mg/kg BW/h. The selected anaesthetic regime was used throughout the operation. After induction of anaesthesia, a central venous line and urinary catheter were inserted in all patients.

We gave 1 mg/kg of heparin to achieve an activated coagulation time (ACT) of 250 seconds or more before the surgeon commenced the sewing of anastomoses and manipulations of the heart. At the end of the operation, heparin was neutralised with protamine sulphate according to the 1:0.8 ratio (i.e., 0.8 mg protamine for 100 IE heparin), until the pre-anaesthesia ACT was reached. Surgical access to the heart was always via a sternotomy incision. The left internal mammary artery was dis-

placed from the thoracic wall to perform the bypass on the left coronary artery (LAD) or its branches, and the saphenous vein taken. All the off-pump procedures were performed by the same surgeon (the fifth author) and the anaesthesiologist was also always the same person (the first author).

We directly monitored arterial pressure, central venous pressure, urine output per hour, 12 channel ECG, temperature, FiO2, capnography, blood gasses and pulse oxymetry during surgery in all patients. Haemodynamic monitoring included the Advanced Minimally Invasive Monitoring (Edwards Lifesciences). When used with Flo-Trac sensor and Pre-Sep catheter, the Vigileo monitor measures and displays key flow parameters (Cardiac output – CO, Stroke volume – SV, Stroke volume variation – SVV, Systemic vascular resistance – SVR) and continuous central venous oxygen saturation (ScvO2), thus being a single-monitor solution for fluid optimisation and tissue oxygenation.

If the patients showed signs of systemic hypotension during the manipulations of the heart, we first directed the surgeon's attention to it;communication between the surgeon and the anaesthesiologist is essential during off-pump heart surgery. The surgeon would then reposition the heart and wait for the patient to stabilise. Then we would infuse fluids or blood if needed, or give vasoactive or inotropic and antiarrhythmic drugs. There was no need to initiate CPB in any patient.

After the operation, propofol and sevoflurane were discontinued and patients were transferred to the intensive care unit (ICU). Fast-tracked awakening and extubation followed. Patients were given fentanyl during the operation for analgesia, and piritramide 45 mg/50 ml infusion 2.3 ml/hour (as well as paracetamol 1 g/8 hours if needed) in the ICU. All patients were weaned from the respirator and extubated within 6 hours of the end of the operation and transfer to the ICU. There were no reoperations because of bleeding or any other complications.

Blood samples and biochemical analyses

To quantify ischaemic myocardial injury, we measured troponin I (ADIVA Centaur XP, Siemens, Germany). Cystatin C was determined to indicate renal dysfunction (cystatin C ELISA test). All analyses were performed at the Clinical Institute for Chemistry and Biochemistry of the University Medical Centre Ljubljana. Blood samples were taken at the following eight time-points:

- before induction of anaesthesia;
- during cross-section of the pericardium;
- upon completion of the distal coronary anastomoses;
- upon reperfusion;
- 30 minutes after admission to the ICU;
- 12 hours after admission to the ICU;
- 24 hours after admission to the ICU;
- 48 hours after admission to the ICU.

Statistical analyses

The sample size for the study was determined based on a simplistic univariate analysis aiming to prove a difference between the two groups of 0.25 μg/L in the average troponin I value at a selected time-point with 80% power at 5% alpha level, assuming a standard deviation of 0.35 μg/L within each group.

We first tested the successfulness of randomisation by comparing relevant baseline characteristics (age, LVEF – left ventricular ejection function, EURO score and weight) using the independent-samples t-test. In the main analyses of both blood parameters we tested the differences between the two groups of the mean values over time using the mixed-model analysis of variance (ANOVA). Before ANOVA, the measurements were log-transformed, which reduced the asymmetry of the distributions and homogenised the variances. We first conducted three-way 2×2×8 ANOVA, whereby group and sex were the between-subject (with 2 levels each) factors and time was the within-subject factor (with 8 levels). Because neither the main effect of sex nor the interaction effects including sex were statistically significant, we subsequently pooled the men and women and conducted a two-way 2×8 ANOVA (with group and time as the factors). Whenever Mauchly's test indicated statistically significant departure from the assumption of sphericity, the Greenhouse-Geisser correction was applied to the tests of within-subject effects (as evidenced by non-integer degrees of freedom, df, reported in the results). We did not conduct post-hoc analyses after ANOVA, but we tested for trend over time using polynomial contrasts.

We also summarised the time-course with two parameters for each analysed substance for each patient. For troponin I, we calculated the range (i.e., the difference between the highest and the lowest measurement), and the ratio between the 6th and the 4th measurement (when the largest rise typically occurs). For cystatin C, we calculated the median and the range. We analysed those parameters using two-way between-subjects 2×2 ANOVA with group and sex as the two factors.

- Statistical significance was set at $p \leq 0.05$.
- Statistical analyses were performed using IBM SPSS Statistics for Windows 20 (IBM Corp., Armonk, NY, 2011).

RESULTS

The baseline characteristics of the patients are summarised in table 1. The lack of statistically significant differences indicates that randomisation was successful and that the two groups could be validly compared.

The distributions of the measurements are depicted in figures 2 and 3 for troponin I and cystatin C, respectively. The mixed-model analyses of variance are summarised in table 2.

The lack of a statistically significant effect of sex ($F1,58=0.19$, $p=0.666$ for troponin and $F1,58=2.95$, $p=0.091$ for cystatin C) or any of the interactions involving sex (group×sex: $F1,58=0.96$, $p=0.331$ for troponin and $F1,58=3.53$, $p=0.065$ for cystatin C; time×sex: $F2.71,157.21=0.84$, $p=0.466$ for troponin and $F3.73,216.21=0.85$, $p=0.487$ for cystatin C; time×group×sex: $F2.71,157.21=0.30$, $p=0.804$ for troponin and $F3.73,216.21=0.32$, $p=0.853$ for cystatin C) justified its omission as a factor from further analyses. The effect of time proved to be highly statistically significant for both blood parameters ($F2.71,157.21=201.48$, $p<0.001$ for troponin; $F3.73,216.21=6.37$, $p<0.001$ for cystatin C). For the majority of patients, the troponin I measurements remained at the initial level until reperfusion, then rose quickly and reached a peak 12 hours after admission to the ICU, descending approximately back to the reperfusion level 48 hours after admission to the ICU. For cystatin C, the time-course was rough-

ly the opposite, thus approximately bath-shaped, only with relatively smaller changes. For both blood parameters, quadratic contrasts were statistically significant for time ($F_{1,58}=106.83$, $p<0.001$ for troponin and $F_{1,58}=28.82$, $p<0.001$ for cystatin C).

For the calculated parameters, distributions are depicted in figure 4 and the analyses of variance are summarised in table 3. No statistically significant effect was found (all p-values were >0.05; F statistics, associated degrees of freedom and p-values are listed in table 3).

Table 1. Baseline characteristics of the two patient groups.

Characteristic	Sevoflurane group	Propofol group	p
Age [years; mean (SD)]	67.1 (10.0)	65.2 (9.7)	0.450
LVEF [%; mean (SD)]	49% (14%)	53% (11%)	0.305
LVEF [no. with deteriorated / normal heart function]	6 / 25	7 / 24	1.000
euroSCORE [points; mean (SD)]	2.1% (2.0%)	1.9% (2.0%)	0.805
Weight [kg; mean (SD)]	86.2(19.6)	80.3(14.9)	0.188
Sex [no. female / male]	9 / 22	9 / 22	NA

LVEF, left ventricular ejection function; NA, not applicable (balanced by design).

Table 2. Summary of the mixed-model analyses of variance for the measurements.

Blood parameter	Model	Effect	p
Troponin I	Three-way	Time	<0.001
		Group	0.788
		Sex	0.666
		Time × Group	0.427
		Time × Sex	0.466
		Group × Sex	0.331
		Time × Group × Sex	0.804
	Two-way (men and women pooled)	Time	<0.001
		Group	0.452
		Time × Group	0.351
Cystatin C	Three-way	Time	<0.001
		Group	0.822
		Sex	0.091
		Time × Group	0.716
		Time × Sex	0.487
		Group × Sex	0.065
		Time × Group × Sex	0.853
	Two-way (men and women pooled)	Time	<0.001
		Group	0.285
		Time × Group	0.544

Table 3. Summary of the two-way between-subjects analyses of variance for the calculated parameters.

Blood parameter	Calculated parameter	Effect	F	df	p
Troponin I	Maximum difference	Group	0.30	1, 58	0.583
		Sex	1.17	1, 58	0.283
		Group × Sex	0.37	1, 58	0.545
	Ratio between 6th and 4th measurement	Group	0.02	1, 58	0.879
		Sex	0.15	1, 58	0.700
		Group × Sex	1.09	1, 58	0.301

Cystatin C	Median of measurements	Group	0.03	1, 58	0.872
		Sex	3.21	1, 58	0.078
		Group × Sex	3.09	1, 58	0.084
	Range of measurements	Group	0.00	1, 58	0.973
		Sex	1.43	1, 58	0.237
		Group × Sex	0.05	1, 58	0.829

DISCUSSION

Our randomised trial compared the effect of sevoflurane- and propofol-maintained anaesthesia on troponin I and cystatin C concentrations in patients undergoing off-pump heart surgery.

The study was balanced by sex and no statistically significant influence of sex on the release of either troponin I or cystatin C was observed. Women had long been excluded from such clinical trials because coronary artery disease had been a men's domain; but it was shown that female sex is associated with increased length of stay after coronary artery bypass surgery because of the advanced age at which women face coronary disease, higher incidence of comorbidities compared with men when they need bypass surgery, lower body size and narrower coronary vessels with difficult access. (14-15) There may be a difference in myocardial structural proteins between the sexes, and hence a difference in response to ischaemia and reperfusion injury. Schwarzenberger and co-workers observed greater release of troponin I in men than in women during on-pump coronary artery bypass surgery. (16) Women also wake faster following general anaesthesia and differ from men in their postoperative recovery as reflected by postoperative pain, nausea and vomiting, and overall quality of recovery. Female sex hormones may play a role in modulating the beneficial and adverse effects of general anaesthesia. (17) Nevertheless, we observed no clear differences between men and women in our study, and therefore pooled them for subsequent analyses in order to gain statistical power.

No statistically significant difference was found between the two anaesthetic regimes either in the overall level of blood parameters (which would correspond to the main effect of the group) or in the shape of the time-course of the blood parameters (which would correspond to a group×time interaction effect). The analyses of the calculated parameters, which might efficiently summarise the time-course and reduce the random inter-patient variation, confirmed this finding. According to De Hert and co-workers, (8) the anaesthetic regime used in our study was most protective throughout the surgical procedure. De Hert also highlighted that the relationship between the dose of volatile anaesthetic that is sufficient to provide general anaesthesia and the dose that could provide protection from ischaemic injury, as well as the exact time of administration to achieve cardioprotection, is still not known, whereby a prohibitively high number of patients would be needed to resolve those questions. (18). Similarly, a recent systematic review pointed out that not all studies have demonstrated improved outcomes as a result of using volatile anaesthetics as cardioprotective agents in patients undergoing coronary artery bypass graft surgery. (19)

Conzen and co-workers used the principle of the two regimes of anaesthesia throughout the procedure in off pump heart surgery and observed lower troponin I release as well as diminished inflammatory process when sevoflurane was administered. (20) Landoni and co-workers reviewed the protective role of volatile anaesthetics desflurane and sevoflurane in randomised clinical trials and argued that volatile anaesthetics could reduce the postoperative release of cardiac troponin I, the need for inotropic support, and the number of patients requiring prolonged hospitalisation following coronary artery bypass graft surgery either with or without cardiopulmonary bypass. (11)

Off-pump heart surgery is associated with lower risk of developing acute kidney injury than on-pump heart surgery, and may be one of the factors that offer better survival outcomes after coronary artery surgery. The risk of death increases with the rising degree of renal injury . (21,22) The overall index of kidney function is provided by glomerular filtration rate (GFR). Cystatin C has been suggested to be an endogenous marker of GFR. It does not change with age or muscle mass and is not influenced by protein in the diet. However, a study has demonstrated that older age is associated with higher serum cystatin C levels. (23) Stevens and co-workers suggest that serum cystatin C may be a better predictor of outcomes of cardiovascular disease than GFR estimates based on levels of serum creatinine. (23-24) Serum cystatin C concentration is related to weight and height as well as to smoking status and C-reactive protein and steroid presence, rises proportionally when GFR decreases and is susceptible to small deteriorations in renal function. (23-24)

In our study a shallow bath shape of the time-course of cystatin serum concentration was observed in both groups. Somewhat higher, but not statistically significantly, average cystatin C values were observed in the sevoflurane group (in which two patients had very high values). Most importantly, all the observed values of cystatin C were within the normal range for all patients, thus suggesting maintenance of normal kidney function during and after myocardial revascularisation on the beating heart.

Vives concluded that acute kidney injury was a major perioperative complication after cardiac surgery, associated with significant morbidity and mortality and related costs, but no preventive strategies had been suggested. Early treatment with renal replacement therapy may improve outcomes after heart surgery. (12) Seabra and co-workers published results of a meta-analysis of 22 trials comparing on-pump to off-pump heart surgery regarding acute kidney injury, and found that off-pump surgery might be associated with a lower incidence of acute kidney injury but had no effect on dialysis requirement or all-cause mortality. (26)

To summarise, we were unable to confirm the hypothesis that sevoflurane protects the heart more effectively than propofol in myocardial revascularisation without the use of cardiopulmonary bypass. Our

patients were all aged about 65 years, had good ventricular function and a low EURO score. It is likely that the characteristics of the patients in our sample precluded the possibility of detecting a substantial difference between the two anaesthetic regimes concerning either myocardial or kidney function. It should also be emphasised that all patients were operated by the same surgeon and that the anaesthesiologist was also the same in all cases.

Hence, our randomised trial showed no clear superiority of either the sevoflurane or propofol anaesthetic regime in off-pump myocardial revascularisation in regard to either heart protection, as reflected in troponin I concentration, or kidney protection, as reflected in cystatin-C concentration. We therefore support both options for future clinical use.

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