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Comparison of the cardioprotective effects of dexmedetomidine and remifentanil in cardiac surgery*

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Background/aim: Myocardial protection is an important factor of open heart surgery and biological biomarkers (lactate, CKMB, cardiac troponin I, and pyruvate) are used to assess myocardial damage. This study compares the effects of dexmedetomidine and remifentanil on myocardial protection during coronary artery bypass grafting (CABG) surgery.

Materials and methods: Patients scheduled for elective CABG surgery (n = 60) were included in this study. Anesthesia induction was introduced with propofol, fentanyl, and vecuronium bromide. Anesthesia was maintained with remifentanil infusion and sevoflurane in the remifentanil group (Group R) and with dexmedetomidine infusion and sevoflurane in the dexmedetomidine group (Group D). Blood samples for biochemical markers were taken from the coronary sinus catheter before cardiopulmonary bypass (T1), 20 min after aortic cross-clamping (T2), 20 min after removal of the aortic cross-clamping (T3), and 10 min after separation from cardiopulmonary bypass (T4).

Results: Demographic data were similar between the groups. Lactate level at the T2 period and CKMB levels during the study period were lower in Group D than in Group R. In both groups, all values except pyruvate significantly increased over time.

Conclusion: The dexmedetomidine-sevoflurane combination may improve the cardioprotective effect in comparison with remifentanil-sevoflurane in CABG surgery.

Key words: Dexmedetomidine, myocardial protection, remifentanil, sevoflurane

1. Introduction

Myocardial protection is important in preventing the damaging effects of a cardiopulmonary bypass (CPB) on the myocardium, including ischemic and reperfusion injury (1). Eliminating or reducing myocardial injury can improve the clinical prognosis of patients undergoing cardiac surgery. Cardiac biomarkers are associated with the degree of cardiac injury and cardiac troponin I (cTnI), lactate, and creatine phosphokinase-MB (CKMB) are especially sensitive biomarkers for evaluating cardiac cell damage (2–4). Pyruvate, lactate, glucose, and insulin are respiratory substrates indicating heart perfusion. The level of pyruvate in the blood increases in the anaerobic state and pyruvate is converted to lactate under these conditions (3–5).

Sevoflurane, a potent inhalation agent, decreases the inflammatory response and improves myocardial function after CPB (6). Dexmedetomidine, a selective and specific α-2 adrenoceptor agonist, has been frequently used as a sedative or adjuvant anesthetic drug in cardiac surgery. Dexmedetomidine has also been known to have some neuroprotective effects; however, data are insufficient for its cardioprotective effects in human studies. Remifentanil, a fast-acting opioid, has been generally used in cardiac surgery for cardiac protection before sternotomy (7).

This study compared the cardiac effects of sevoflurane plus dexmedetomidine with those of sevoflurane plus remifentanil during adult cardiac surgery with CPB by examining levels of lactate, pyruvate, CKMB, and cTnI in patient blood samples. The hypothesis is that a difference

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would be seen between dexmedetomidine and remifentanil as an adjuvant anesthetic drug for cardiac surgery in terms of their myocardial protective effects.

2. Materials and methods

2.1. Patients

After approval by the local ethics committee (Çukurova University; 20 June 2013; Approval No. 20/9) and clinical trials (NCT02405689), written informed consent was obtained from the patients (n = 60) for this prospective randomized study conducted between December 2014 and August 2015. The patients were between the age of 18 and 70 years, scheduled for elective CABG surgery, and had physical status of II–III according to the American Society of Anesthesiologists. The exclusion criteria were emergency surgery, prior cardiac surgery (reoperation), ejection fraction less than 50%, moderate or severe chronic restrictive or obstructive pulmonary disease, hypoxia (SpO_2 < 90% in room air), preoperative mechanical ventilation, intraaortic balloon pump, inotropic agent requirement, chronic liver disease, or renal failure (creatinine > 1.6 mg/dL), bradycardia (heart rate < 50 beats/min), chronic atrial fibrillation, or elevated levels of cardiac enzyme within 48 h before surgery.

All preoperative cardiac medication was continued until the day of surgery. Premedication was provided intravenously (iv) with 0.02 mg/kg midazolam to all patients 30 min before surgery. A five-lead electrocardiogram, invasive arterial blood pressure, and pulse oximetry monitoring were applied to all patients in the operating room. After 2 mL of 0.2% lidocaine was injected subcutaneously, a radial arterial catheter was inserted for continuous blood pressure monitoring.

Anesthesia was induced with 1 mg/kg propofol iv and 1 μg/kg fentanyl iv for all patients. Vecuronium bromide (0.1 mg/kg) was given to facilitate endotracheal intubation and additional doses of 0.03 mg/kg were administered during CPB. A central venous catheter (internal jugular or subclavian) and an esophageal heat probe were inserted after tracheal intubation. The same surgery team operated on all the patients. The surgeries took place under cardiac arrest with CPB. The surgical steps were standardized with median sternotomy and pericardiotomy. Methylprednisolone (5 mg/kg) was administered to decrease the CPB-related inflammatory response in all patients. Unfractionated heparin (300 U/kg, iv) was given to achieve an activated clotting time (ACT) of more than 480 s during CPB. If the ACT was less than 480 s, an additional dose of heparin (100 U/kg) was given during CPB. CPB was started after aortic and venous cannulas had been inserted. Myocardial protection was achieved with intermittent blood cardioplegia, repeated in intervals of 20–25 min. We drew 400 mL of blood from the heart–lung pump and potassium chloride was added to the cardioplegia solution as K^+ level 16 mEq/L. There was no additional drug (such as $NaHCO_3$ or mannitol) in the cardioplegia solution, except potassium. The amount of potassium chloride added was calculated with the following formula:

added potassium (mEq) = [16 – measured potassium (mEq/L)] × 0.4.

An antifibrinolytic agent (aprotinin or tranexamic acid) was not used during the surgery. At the end of the CPB, 1.5 mg of protamine sulfate (iv) per 100 U of iv heparin was used to reverse the anticoagulation effect.

The patients were divided into two groups with computer-generated randomization: a remifentanil group (Group R, n = 30) and a dexmedetomidine group (Group D, n = 30). In Group R, anesthesia was maintained with 0.5%–1.5% sevoflurane in a 50%/50% oxygen/air mixture and 0.125–0.25 μg/kg/min remifentanil infusion after a 1 μg/kg/10 min loading dose of remifentanil. In Group D, anesthesia was maintained with 0.5%–1.5% sevoflurane in a 50%/50% oxygen/air mixture and 0.3–0.9 μg/kg/min dexmedetomidine infusion after a 0.5 μg/kg/10 min loading dose of dexmedetomidine. The drugs were diluted to 100 mL in 0.9% NaCl (the final volume was 100 mL = drugs + NaCl), and the prepared infusions were given to the patients by an investigator blinded to the patients' group designations. The infusions were discontinued at the end of the surgery and the patients were transferred to the intensive care unit intubated and fully monitored.

Nitroglycerin infusion (0.5–2 μg/kg/min) was used for all patients during CPB and the infusion rate was titrated to maintain a mean perfusion pressure of 50–80 mmHg. During the rewarming period, 0.2 mg/kg midazolam was administered to the patients. Hematocrit values were maintained at 25%–28% during the CPB period and above 30% in the post-CPB period. The nitroglycerin infusion, sevoflurane concentration, fluid replacement, and ephedrine rates were adjusted to maintain optimal blood pressure (mean arterial pressure = 50–65 mmHg) during CPB, if needed. After CPB, fluid replacement was performed and dopamine infusion (5–10 μg/kg/min) was started if the mean arterial pressure dropped below 60 mmHg according to clinical conditions.

Mean arterial pressure (MAP) and arterial blood gas analysis were observed and recorded during surgery. All blood samples, including lactate, pyruvate, CKMB, and cTnI, were taken via the coronary sinus catheter at specific times. The aortic cross-clamping time, CPB time, extubation time, and length of stay in the intensive care unit (ICU) and hospital were recorded.

2.2. Blood samples

Blood samples for biochemical markers were taken from the patients via coronary sinus catheter at four time-

points: before CPB (as soon as the coronary sinus catheter was inserted, T1), 20 min after aortic cross-clamping (T2), 20 min after removal of the aortic cross-clamping (T3), and 10 min after separation from CPB (T4).

The blood samples were drawn from the patients and collected in EDTA tubes and 5-mL vacuum collection tubes without anticoagulant for serum separation (Becton Dickinson Vacutainer, Ref. 369032) under standardized conditions to minimize sources of preanalytical variation. All blood samples with visible hemolysis were discarded.

The EDTA samples (under appropriate conditions) were used for the lactate test without waiting. The tubes without anticoagulant were allowed to clot at room temperature for 15–20 min, separated by centrifugation at 3000 × *g* for 10 min, and kept refrigerated if analyzed within 12 h. Otherwise, the samples were frozen at −80 °C and analyzed within 1 year. When all of the specimens were available, they were thawed, mixed, centrifuged again at 3000 × *g* for 10 min, and then analyzed at room temperature.

The lactate plasma analyte was analyzed colorimetrically. The analysis was performed with a Beckman Coulter kit (Cat. No. 445875) on the Beckman UniCel DXC 800 Synchron autoanalyzer (Beckman Coulter Inc., CA, USA). The cTnI and CKMB serum analytes were analyzed via chemiluminescent immunoassay. The analysis was performed with Beckman Coulter kits (Cat. No. A78803 and Cat. No. 386371, respectively) on the Beckman Coulter Access 2 Immunoassay System fully automatized autoanalyzer (Beckman Coulter Inc.). Finally, the pyruvate serum analyte was analyzed with a colorimetric assay (λ = 570 nm). The analysis was carried out with a pyruvate assay kit (Cat No. ab65342, Abcam, Cambridge, UK) and BioTek Instruments (Winooski, VT, USA). The detection range of this kit was 40–200 μM, version 9, last updated 30 April 2015 (www.abcam.com).

2.3. Statistical analysis

All analyses were performed using SPSS 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean ± SD and as median plus minimum–maximum where appropriate. The chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Kolmogorov–Smirnov test. For comparison of continuous variables between two groups, Student's t-test or the Mann–Whitney U test were used, depending on whether the statistical hypotheses were fulfilled or not. To evaluate the change in lactate, CKMB, cTnI, and pyruvate levels over time, repeated measurements analysis was applied. The statistical level of significance for all tests was set to 0.05.

2.4. End points

The primary end points were the blood levels of lactate, pyruvate, CKMB, and cTnI. The secondary end points were extubation time and length of stay in the ICU.

3. Results

Demographic data (age, sex, and weight), duration of CPB, aortic cross-clamping time, extubation time, length of ICU and hospital stay, and arterial blood gas analyses were similar between the groups (P > 0.05) (Tables 1 and 2).

In both groups, coronary sinus lactate release increased progressively over time (P < 0.001 and P = 0.006), but it was higher in the T2 period in Group R than in Group D (P = 0.03) (Table 3).

Table 1. Demographic data, CPB, and cross clamping time of the groups.

	Group R (n = 30) (mean ± SD)	Group D (n = 30) (mean ± SD)	P
Age (years)	53.90 ± 15.43	59.83 ± 14.22	0.13
Sex (female/male)	9/21	13/17	0.42
Weight (kg)	75.33 ± 13.31	76.93 ± 16.27	0.68
CPB time (min)	119.60 ± 34.77	114.33 ± 34.88	0.56
Cross clamping time (min)	78.36 ± 21.66	74.00 ± 25.83	0.48
Extubation time (h)	6.23 ± 3.98	6.73 ± 3.48	0.61
Length of ICU stay (day)	3.50 ± 2.62	3.16 ± 0.98	0.52
Length of hospital stay (day)	8.86 ± 3.10	10.60 ± 4.08	0.07

Data are presented as mean ± SD (standard deviation) or as the number of patients. Group R: Remifentanil group; Group D: dexmedetomidine group; CPB: cardiopulmonary bypass; ICU: intensive care unit.

Table 2. Mean arterial pressure and arterial blood gas analysis of the groups.

	Group R (n = 30) (mean ± SD)	Group D (n = 30) (mean ± SD)	P
MAP			
T1	65.30 ± 11.55	67.27 ± 14.04	0.68
T2	59.13 ± 9.92	58.97 ± 9.32	0.87
T3	54.07 ± 13.20	57.10 ± 9.85	0.38
T4	65.00 ± 8.10	64.60 ± 7.98	0.87
pH			
T1	7.38 ± 0.07	7.34 ± 0.06	0.49
T2	7.34 ± 0.05	7.30 ± 0.06	0.54
T3	7.33 ± 0.05	7.31 ± 0.05	0.73
T4	7.32 ± 0.06	7.29 ± 0.07	0.95
PaO_2			
T1	211.87 ± 69.30	186.54 ± 75.85	0.18
T2	254.80 ± 53.70	268.17 ± 44.40	0.30
T3	255.83 ± 53.77	267.13 ± 39.82	0.36
T4	200.31 ± 85.40	189.78 ± 91.92	0.65
$PaCO_2$			
T1	35.15 ± 5.46	33.77 ± 5.55	0.79
T2	36.50 ± 3.25	35.95 ± 3.52	0.79
T3	36.00 ± 2.86	35.28 ± 3.74	0.26
T4	35.46 ± 5.65	35.58 ± 4.37	0.27
HCO_3			
T1	21.50 ± 2.18	19.37 ± 3.02	0.21
T2	20.25 ± 1.92	18.59 ± 2.47	0.41
T3	19.23 ± 1.49	18.49 ± 1.73	0.50
T4	18.25 ± 1.52	17.61 ± 2.26	0.23

Data are presented as mean ± SD (standard deviation). Group R: Remifentanil group; Group D: dexmedetomidine group; MAP: mean arterial pressure; T1: before CPB; T2: 20 min after aortic cross-clamping; T3: 20 min after removal of the aortic cross-clamping; T4: 10 min after separation from CPB.

CKMB levels were raised in both groups ($P < 0.001$ and $P = 0.008$), but this rise was significantly higher in Group R than in Group D at the four time-points ($P = 0.03$, $P = 0.01$, $P = 0.04$, and $P = 0.03$, respectively) (Table 3).

cTnI release increased consistently in both groups over time ($P < 0.001$ and $P = 0.011$) and there were no significant differences between the groups ($P > 0.05$) (Table 3).

Finally, the pyruvate levels remained unchanged during the sampling period and no differences were seen between the groups ($P > 0.05$) (Table 3).

4. Discussion

In this study comparing two anesthetic techniques, the CKMB levels in all study periods and the lactate levels in the T2 period were lower in the sevoflurane-dexmedetomidine group than in the sevoflurane-remifentanil group. However, no differences were seen in extubation time, length of ICU, or hospital stay.

Cardiac surgery with the CPB procedure is associated with ischemia/reperfusion injury. Some techniques should be performed to prevent organ injury, such as systemic and/or topical hypothermia. One such method is cardioplegia, which minimizes myocardial damage during this stressful period. In addition, the choice of anesthetic agent may help in cardiac protection. Balanced anesthesia techniques (a potent volatile anesthetic and an adjuvant agent) are generally performed for fast-track adult cardiac surgery. Therefore, balanced anesthesia techniques with sevoflurane-remifentanil and sevoflurane-dexmedetomidine were selected for this study.

Cardiac biomarkers cTnI, lactate, and CKMB can be indicators of cardiac injury, and coronary sinus blood sampling can be used to evaluate early myocardial release for these cardiac biomarkers (2–4). In particular, cTnI is a highly specific and sensitive biomarker for myocardial cell injury (2). Kapoor et al. showed that pyruvate is a myocardial

Table 3. Lactate, CKMB, cTnI, and pyruvate values of the groups.

	Group R (n = 30), median (min–max)	Group D (n = 30), median (min–max)	P
Lactate (mmol/L)			
T1	2.95 (1.45–14.60)	2.40 (1.14–22.26)	0.10
T2	4.30 (2.07–14.80)	3.13 (1.40–15.10)	0.03*
T3	4.50 (2.10–12.50)	4.19 (1.55–23.46)	0.38
T4	4.40 (2.04–15.00)	3.95 (1.61–27.45)	0.35
P	<0.001*	0.006*	
CKMB (mg/L)			
T1	5.30 (0.01–18.00)	2.60 (1.60–31.60)	0.03*
T2	11.75 (1.30–155.70)	5.80 (2.60–194.30)	0.01*
T3	22.75 (3.00–82.80)	15.00 (5.10–250.90)	0.04*
T4	30.60 (5.40–91.30)	20.25 (9.30–97.20)	0.03*
P	<0.001*	0.008*	
cTnI (mg/L)			
T1	0.15 (0.00–2.09)	0.07 (0.01–31.18)	0.40
T2	0.50 (0.06–11.20)	0.20 (0.05–28.32)	0.33
T3	1.03 (0.18–14.61)	1.07 (0.21–30.02)	0.91
T4	1.90 (0.30–11.59)	1.29 (0.33–34.51)	0.70
P	0.001*	0.011*	
Pyruvate (mmol/L)			
T1	0.02 (0.01–0.03)	0.01 (0.01–0.05)	0.74
T2	0.02 (0.01–0.07)	0.02 (0.01–0.05)	0.71
T3	0.03 (0.01–0.09)	0.02 (0.02–0.09)	0.52
T4	0.03 (0.01–0.09)	0.02 (0.01–0.06)	0.24
P	>0.05	>0.05	

Data are presented as median (min–max). CKMB: Creatine phosphokinase-MB; cTnI: cardiac troponin I; T1: before CPB; T2: 20 min after aortic cross-clamping, T3: 20 min after removal of the aortic cross-clamping; T4: 10 minutes after separation from CPB. *: Statistically significant.

biomarker for predicting postoperative outcome along with lactate, cTnI, and CKMB (3). In addition, they claimed that pre-CPB myocardial lactate (2.9 mmol/L) and pyruvate (0.07 mmol/L) levels can be used to estimate the post-CPB inotropic agent requirement (3). With this in mind, pyruvate was added to cTnI, lactate, and CKMB as a cardiac biomarker from the coronary sinus blood samples in our study. Although the lactate values were higher than 2.9 mmol/L and the pyruvate values were lower than 0.07 mmol/L in both groups, the extubation time, length of ICU and hospital stay, and inotropic requirements were similar between the groups in this study.

Dexmedetomidine may be used as an adjuvant anesthetic drug during cardiac surgery. It is preferred due to its antiarrhythmic, cardioprotective, delirium therapeutic, and analgesic effects (8). Several animal studies have shown that dexmedetomidine protects against ischemia/reperfusion injury in the heart, brain, kidneys, and lungs (9–13). It may also improve the coronary artery blood flow and reduce lactate levels in ischemia models in animals (13–15). Okada et al. demonstrated that dexmedetomidine improved global infarct size in a rat heart model (13). Ji et al. showed an improvement in mortality rate with iv dexmedetomidine infusion in patients undergoing CABG surgery (9). Riha et al. found that the coadministration of dexmedetomidine-ketamine was associated with lower blood levels of cTnI and CKMB than sevoflurane-sufentanil anesthesia in patients undergoing elective CABG surgery (16).

Opioids are commonly used as adjuvant anesthetic drugs in cardiac surgery. Recently, opioids have been shown to provide an opioid-induced cardioprotection via the δ-opioid receptor on cardiac myocytes (17–19). In some animal and human studies, the δ-opioid receptor stimulation produced K-dependent ATP channel activation, and this mechanism seems to be responsible for

the potent cardioprotective effect (20–22). Moreover, Irwin et al. stated that cardiac opioid receptors (delta-1, kappa) are responsible for opioid-induced cardioprotection via protein kinase C activation and the potassium channel (23).

Remifentanil may be useful for cardiac patients due to its rapid elimination and noncumulative effect properties. Wong et al. showed that several cardiac biomarkers (creatine kinase, cTnI, ischemia-modified albumin, heart-type fatty acid-binding protein, etc.) decreased in cardiac patients using remifentanil (7). When comparing the cardiac protective effect of remifentanil with fentanyl, lower CKMB and troponin T levels were observed with remifentanil (24,25). In this study, CKMB levels and lactate levels at T2 were lower in the sevoflurane-dexmedetomidine group than in the sevoflurane-remifentanil group at all times. However, no differences were seen between the groups for the other values.

This study has certain limitations. First, blood samples were taken through a coronary sinus catheter for more accurate early information. Consequently, the intraoperative and postoperative levels of lactate, pyruvate, cTnI, and CKMB values were not compared. Therefore, the effects of dexmedetomidine and remifentanil on postoperative biomarkers could not be investigated. Moreover, only patients from a certain time period (December 2014–August 2015) were included this study; for this reason, the sample size was small (n = 60). Finally, the echocardiographic comparison of the groups could be useful for determining myocardial function after CPB.

In conclusion, the sevoflurane-dexmedetomidine combination may produce more improved cardioprotective effects compared with sevoflurane-remifentanil anesthesia. Further prospective, multicenter, and randomized studies with larger sample sizes are needed to compare the cardioprotective effects of dexmedetomidine to those of opioids.

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