A comparison of total intravenous anesthesia, sevoflurane, and isoflurane anesthesia for preconditioning in cardiac surgery

Kardiyak cerrahide önkoşullama için total intravenöz anestezi, sevofluran ve izofluran anestezilerinin karşılaştırılması

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Background: In this study we compared the myocardial protective effects of fentanyl-based total intravenous anesthesia (TIVA), sevoflurane and isoflurane.

Methods: After ethic committee approval, 57 patients who were scheduled to undergo open heart surgery using cardiopulmonary bypass (CPB) were randomized into three groups. Following standard induction, group 1 (TIVA group; n=17) received fentanyl-midazolam-pancuronium, group 2 (Sevo group; n=20) received 1 MAC sevoflurane and group 3 (Iso group; n=20) received 1 MAC isoflurane for maintenance. During preoperative period and on postoperative third day, left ventricle functions and cardiac scores were evaluated by transthoracic echocardiography. Cardiac troponin I (cTnI) and creatine kinase MB fraction (CKMB) were measured before CPB and at sixth hour, day one, two and three following CPB. For lactate measurement, blood samples were collected from arterial line and retrograde cannula before and after CPB and following declamping.

Results: Demographic parameters were similar among three groups. Cardiac index and output increased in all three groups after CPB. Creatine kinase MB fraction and cTnI levels were similar among groups before CPB, those levels increased in all groups at sixth hour after CPB. Although there was not a statistically significant difference among the groups, this increase was the highest in TIVA group. After declamping, the lactate levels collected from retrograde cannula increased in all groups.

Conclusion: As a result, as all the groups have preconditioning potential, although we did not find a significant difference between fentanyl-based TIVA group and volatile anesthetics in terms of myocardial protection, we could say that volatile anesthetics are more cardioprotective, compared to fentanyl-based TIVA group.

Key words: Ischemic preconditioning; lactic acid; myocardium.

Amaç: Bu çalışmada fentanil bazlı total intravenöz anestezi (TİVA), sevofluran ve izofluranın miyokardiyal koruyucu etkileri karşılaştırıldı.

Çalışma planı: Etik komite onayı alındıktan sonra kardiyopulmoner baypas (KPB) ile açık kalp cerrahisi planlanan 57 hasta üç gruba ayrıldı. Standart indüksiyon sonrası grup 1'de (TİVA grup; n=17) fentanil-midazolam-pankuronyum ile grup 2'de (Sevo grup; n=20) 1 MAC sevofluran ile grup 3'de (Iso grup; n=20) 1 MAC izofluran ile idame yapıldı. Ameliyat öncesi dönemde ve ameliyat sonrası üçüncü günde sol ventrikül fonksiyonları ve kardiyak skorlar transtorasik ekokardiyografi ile değerlendirildi. Kardiyak troponin I (cTnI) ve kreatin kinaz MB fraksiyonu (CKMB) KPB'den önce ve KPB'den sonraki altıncı saatte, birinci, ikinci ve üçüncü günlerde ölçüldü. Laktat ölçümü için kan örnekleri, KPB öncesi ve sonrası ve klempin kaldırılışını takiben arteriyel hattan ve retrograd kanülden alındı.

Bulgular: Demografik parametreler her üç grupta benzer idi. Kardiyopulmoner baypas sonrası kardiyak indeks ve debi her üç grupta da artış gösterdi. Kardiyopulmoner baypas öncesi CKMB ve cTnI seviyeleri gruplar arasında benzer iken, KPB sonrası altıncı saatte bu değerler tüm gruplarda artış gösterdi. İstatistiksel olarak gruplar arasında anlamlı fark olmasa da bu artış TİVA grubunda en yüksekti. Klempin alınmasını takiben retrograd kanülden alınan kan örneklerinde laktat seviyesi tüm gruplarda yükseldi.

Sonuç: Sonuç olarak, bütün grupların önkoşullama potansiyeli olduğundan, miyokardiyal koruma açısından fentanil bazlı TİVA ve volatil anestezik grupları arasında istatistiksel olarak anlamlı bir fark bulamasak da volatil anestezik gruplarının fentanil bazlı TİVA grubuna göre daha kardiyoprotektif olduğunu söyleyebiliriz.

Anahtar sözcükler: İskemik önkoşullama; laktik asit; miyokardium.

Volatile anesthetics have been shown to protect the myocardium from ischemic injury, and the related clinical process has been termed anesthetic-induced preconditioning. The mechanism for anesthetic preconditioning is not clearly understood, but protein kinase, adenosine triphosphate (ATP)-sensitive potassium channels, and adenosine A1 receptors play key roles in this process. The volatile anesthetic, sevoflurane, also increases basal and stimulated coronary flow along with nitric oxide (NO) production.[1] Sevoflurane selectively increases large and small coronary blood flow via mechanisms independent of ATP-sensitive potassium (K_{ATP}) channels.[2] Although clinical studies have demonstrated the translocation of the protein kinase C-δ and € isoform in the human myocardium in response to sevoflurane,[3] conflicting results were found for perioperative ST segment changes, arrhythmias, troponin I (TnI), and creatine kinase-MB isoenzyme (CK-MB) release.[4,5]

Morphine, an opioid, also has preconditioning effects which have been proven by many studies.[6,7] Its protective effect is exercised by way of δ receptor intermediation, and some studies have shown that pure δ opioid agonists may also behave in this way.[7,8] Morphine acts by activating δ receptors, thereby activating K_{ATP} channels and providing cardioprotection. In other studies using remifentanil,[9] fentanyl,[10] and sufentanil as anesthetic agents, it was suggested that besides δ receptors, κ receptors may also contribute to cardioprotection. Although fentanyl has a preferential affinity for μ opioid receptors, it also interacts with δ and κ receptors.[11,12] Kato et al.[12,13] demonstrated that fentanyl has a cardioprotective effect which is mediated by both μ receptors and protein kinase C (PKC) in a model of myocardial ischemia reperfusion (I/R) injury in vitro. Although there are conflicting results regarding the cardioprotective effect of fentanyl,[6] it is one of the most preferred opioid agents due to its reduced side effects. Cardiac anesthesia frequently has a preference for a combination of balanced anesthetic techniques with opioid and volatile anesthetics. This balanced anesthetic technique may enhance protection against myocardial ischemia more than either agent alone. In experimental studies, the combination of isoflurane and morphine provides increased cardiac protection but their clinical effects have not been clearly demonstrated.[14]

Although there are a lot of studies which use fentanyl and volatile anesthetics in balanced anesthesia protocols, fentanyl doses were given in equivalent doses to groups; therefore, only the effects of volatile anesthetics were evaluated.[3,4,15] This study aimed to compare the cardioprotective effects of anesthesia groups using a combination of low-dose fentanyl, sevoflurane, and isoflurane with a fentanyl-midazolam anesthesia group by means of clinical, biochemical, and hemodynamic parameters.

PATIENTS AND METHODS

This study was designed as a double-blinded, randomized study and was performed after obtaining the permission of the ethics committee of Türkiye Yüksek İhtisas Training and Research Hospital, Ankara, Turkey. A total of 57 patients scheduled for elective coronary artery bypass graft surgery (CABG) were enrolled, and informed written consent was obtained from all patients.

Patients under the age of 30 and those older than 75 years old were excluded from the study. Other exclusion criteria were as follows: diabetes mellitus, renal failure, a history of myocardial infarction for at least one month before surgery, preoperative unstable angina pectoris, and patients using theophylline. All patients taken to the operating room were monitored with electrocardiography (ECG), end-tidal carbon dioxide concentration (ETCO2) by capnography, and oxygen saturation (SO2) by pulse oxymetry during the operation. Two peripheral venous catheterizations (16 or 18G needle) and radial artery catheterization with an 18G needle were performed. After local anesthesia, an 8F catheter was placed in the internal jugular vein. A 7F 4-lumen Swan-Ganz catheter (Abbott, TORQUE-LINE 7 F, 110 cm, 1.5 thermo dilution catheter, 4 lumen, RA) was inserted via the jugular catheter.

All patients were premedicated with diazepam (0.1 mg/kg) per os (P.O.) the night before and morphine sulphate (0.1 mg/kg) intramuscular (I.M.) 30 minutes before the operation. An intravenous bolus infusion of midazolam (0.1 mg/kg), fentanyl (15-20 μ/kg), and intravenous pancuronium bromide (0.1 mg/kg) were used in the induction of anesthesia. A tidal volume of 8-10 ml/kg with 50% oxygen-air mixture was achieved with controlled mechanical ventilation after endotracheal intubation.

Hemodynamic parameters were scaled at five different times: T1: Before induction, T2: After induction, T3: Before cardiopulmonary bypass (CPB), T4: After CPB, and T5: Six hours after the operation.

The mean arterial blood pressure (MAP), heart rate (HR), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), cardiac output (CO), cardiac index (CI), stroke volume (SV), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), left ventricular stroke volume index (LVSVI), and right ventricular stroke volume index (RVSVI) were the hemodynamic parameters tested.

Cardiac output was measured with a specific device (3300 Cardiac Output Computer Abbott Laboratories, North Chicago, Illinois, USA).

Patients were randomized into three groups

Group 1 total intravenous anesthesia (TIVA group; n=17): This group was also accepted as a control group. In anesthesia maintenance, fentanyl (0.25-0.5 μg/kg/min) and midazolam (0.3 mg/kg/min) were given by intravenous infusion, and pancuronium was given in a dose of 2 mg as required.

Group 2 sevoflurane (Sevo group; n=20): After the same anesthetic induction procedure as the TIVA group, maintenance doses of fentanyl 5 μg/kg and pancuronium bromide 2 mg were applied repeatedly as required in this group. Sevoflurane was administrated in 1 MAC (minimal alveolar concentration), causing a decrease of approximately 20-25% in the arterial blood pressure.

Group 3 isoflurane (Iso group; n= 20): The procedure was the same as the Sevo group except that the volatile anesthetic agent isoflurane was used instead of sevoflurane.

In groups 2 and 3, the volatile anesthetics were given until CPB was started. After unclamping the aortic cross clamp, the gases were administered again until the end of the operation. In group 1, the agents were infused over the same periods.

A standard CPB technique was performed in all groups. After anticoagulation with routine doses of heparin (400 IU/kg), CPB was started, and a membrane oxygenator (MEDOS Hilite 7000, Vingmed Danmark A/S, Taastrup, Denmark) and a non-pulsatile pump (mean flow= 2.4 L/min/m^2 body surface area) were used. The body temperature was between 32-34 °C during CPB. The heart was arrested by a hyperkalemic crystalloid cardioplegic solution (Plegisol 15 ml/kg) given through anterograde cannula under a pressure of 120 mmHg. During the CPB period, 400 cc of diluted cold blood cardioplegia was applied every 20 minutes, and warm blood cardioplegia was given before unclamping the aortic cross clamp in order to obtain myocardial protection. After unclamping the aorta, CPB was terminated when a rectal temperature of 35-36 °C and adequate cardiac contractions were achieved. At the level of 2.0 L/min/m^2 of CI, inotropic agents were administrated. The inotropic agent requirement, incidence, type, and treatment of postoperative reperfusion arrhythmia were recorded.

Changes in the ST segment on the DII and V5 derivations were recorded electronically on the monitor (Datex Ohmeda S/5, GE Healthcare, Madison, USA)

simultaneously with the hemodynamic parameters. Transthoracic echocardiography was done preoperatively and on the third day postoperatively in order to assess the left ventricular functions, cardiac scores, and ejection fraction (EF).

The biochemical parameters, cardiac troponin I (cTnI) level, and CK-MB fraction were determined at six different times: B1: Before CPB, B2: After CPB, B3: Six hours after surgery, B4: The first day postoperatively, B5: The second day postoperatively, and B6: The third day postoperatively.

For determining the CK-MB levels, blood samples were taken from the patients who had undergone CABG before CPB, after CPB, at the sixth hour postoperatively, and on the first, second, and third days after surgery. Measurements were performed to determine the CK-MB activity with immunologic method by a Hitachi 911 Chemistry Analyzer (Boehringer Ingelheim, Germany).

Cardiac troponin I blood samples were taken from the patients who had undergone CABG before CPB, after CPB, at the sixth hour postoperatively, and on the first, second, and third days after surgery. Cardiac TnI measurements were performed by the Microparticle Enzyme Immunoassay (MEIA) method with an Abbott AxSYM immunoassay diagnostic system in ng/ml (Abbott, Turkey).

Blood samples collected for L-lactate level simultaneously obtained from arterial line and retrograde cannula were examined for lactate levels at two different period: L1: before CPB after the retrograde cannula was placed and L2: after the unclamping of the aorta. For the lactate measurement, 5 ml blood was centrifuged and cooled at –60 °C for eight months. The measurement was done by the enzymatic calorimetric method using the Sigma diagnosis reagent (Procedure No 735) on the Hitachi 911 chemical analyzer (Boehringer Ingelheim, Germany).

Data analysis was performed by using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) for Windows version 11.5 software. Data was shown as mean ± standard deviation for continuous variables and number of patients and percentage (%) for categorical variables. Analysis of variance (ANOVA) or the Friedman test was used to evaluate the differences among repeated measures where applicable. When the *p* value from the repeated measures of ANOVA or Friedman test statistics was statistically significant, Bonferroni adjusted t-tests or Friedman multiple comparison tests were used to know which measurement differed from the others. When the number of repeated

Table 1. Demographics of patients

	Group TIVA		Group Sevo		Group Iso		*Total*	
	n	Mean+SD	n	Mean+SD	n	Mean+SD	n	Mean+SD
Age		49±15		51.4±9.3		50.1±8.8		50.3±11.1
Body surface area (m^2)		1.80±0.17		1.85±0.16		1.83±0.16		1.83±0.16
Gender								
Male	16		18		19		53	
Female	1		2		1		4	
Number of greft		3.2±1.2		2.8±1.0		3.2±0.8		3.0±1.0
Cross clamp time (min)		55.3±26.8		39.8±13.2		42.1±16.4		45.2±19.9
Cardiopulmonary bypass time (min)		79.8±33.9		62.6±22.0		64.8±18.9		68.5±25.9

SD: Stardard deviation.

measures was two, a paired t test was applied to determine whether the differences between the preoperative and postoperative measurements were statistically significant or not. A *p* value of less than 0.05 was considered statistically significant. For all possibilities within group comparisons, the Bonferroni adjustment was applied to control the type I error rate.

RESULTS

Demographic data were given in Table 1. The patients in all three groups were not statistically different in terms of sex, age, body surface area (BSA), American Society of Anesthesiologists (ASA) physical classification, cross-clamp time, and the number of times the patients had undergone CABG and CPB (Table 1). None of the patients developed myocardial ischemia intraoperatively as judged by the automated ST segment analysis, and no patient required a second operation.

There were no significant differences between the groups regarding preoperative cardiac hemodynamic parameters. Neither were the CI values different among the three groups preoperatively. After induction, all patients in the three groups showed similar responses. At the T3 period, there was a significant decrease in the Sevo and Iso group in the SVR measurements compared with the patients in the TIVA group. The CI and CO values were not different between the groups at the T3 period; however, at the T4 period (after CPB measurement), all group values increased significantly over the T3 values, but there were no significant differences between the groups (Table 2).

The incidence of perioperative myocardial ischemic and arrythmic events was assessed with the help of ST segment analysis.

The incidence of arrythmias after cross-clamp release was did not differ among the three groups. In the TIVA group, ventricular fibrillation (VF) was seen in 10 patients (58.8%), and seven patients (41.1%) were defibrillated. In the Sevo group, VF was seen in 12 patients (60%) and eight patients (40%) were defibrillated. Finally, in the Iso group, 11 patients (55%) were diagnosed with VF, and seven patients (35%) needed defibrillation.

Troponin I concentrations were similar in all groups before CPB. After revascularization, the cTnI

Table 2. Haemodynamic parameters

	Groups	T1	T2	T3	T4	T5
		Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Mean arterial pressure (mmHg)	TIVA	102.5±15.35	88.3±13.12	83.9±15.14	65.5±13.41	78.7±9.42
	Sevo	117.2±14.22	90.2±14.65	80.8±16.15	67.5±11.43	85.2±8.53
	Iso	114.3±5.13	86.0±2.65	77.3±20.65	74.3±8.50	69.3±14.01
Cardiac output (L/min)	TIVA	6.2±0.98	4.5±0.88	3.9±0.90	5.4±1.31*	5.3±0.82
	Sevo	6.2±0.76	4.7±1.35	4.3±1.11	5.2±1.08*	6.2±1.29
	Iso	7.5±1.51	5.9±1.07	5.8±0.90	6.4±0.18*	6.3±1.22
Cardiac index (L/min/m^2)	TIVA	3.4±0.58	2.4±0.44	2.2±0.58	2.9±0.78*	2.9±0.48
	Sevo	3.4±0.54	2.5±0.55	2.3±0.56	2.8±0.48*	3.4±0.77
	Iso	3.9±0.42	3.0±0.28	3.0±0.18	3.3±0.41*	3.2±0.34

T1: Before the induction; T2: After the induction; T3: Before cardiopulmonary bypass; T4: After cardiopulmonary bypass; T5: Six hours after the operation; * p≤0.05 according to T3.
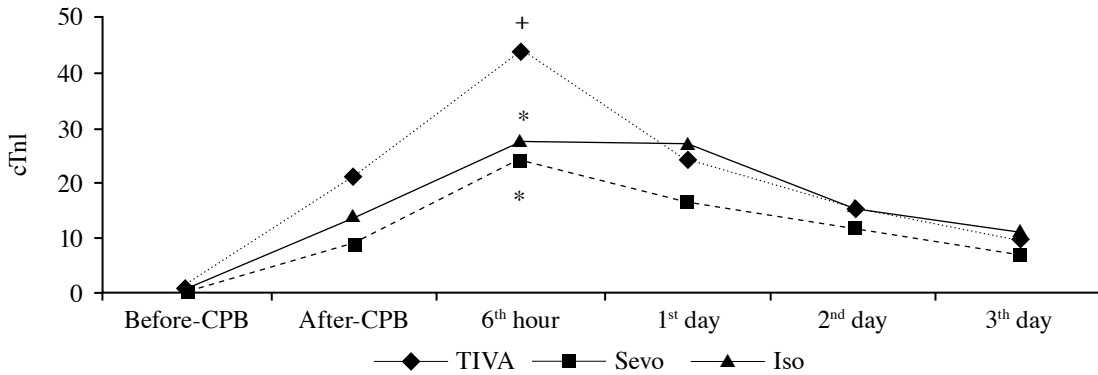
Figure 1. The change in troponin I (as ng/ml). + p<0.001; * p<0.005 compared to before-CPB: Before cardiopulmonary bypass; After-CPB: After cardiopulmonary bypass.

levels increased and reached peak levels at the sixth hour postoperatively. This increase was seen more significantly in the TIVA group (p=0.001) than in the Iso and Sevo groups (p=0.005) in the post-CPB period, but there was no statistically significant difference between the groups. The cTnI levels on the first, second, and third day postoperatively were similar in the Iso and TIVA groups but were lower in the Sevo group. No statistical significance between groups was evident (Figure 1).

The creatinine kinase-myocardial fraction measurement results were also comparable at the beginning of surgery and all groups' data were similar to each other. These levels were significantly different in the postoperative periods in all groups compared with the basal (preoperative) levels. At the sixth hour, this significance was very high (p=0.001) compared with the baseline in all groups, but CK-MB results at the sixth hour and first day postoperatively were not significantly different between the groups (Figure 2).

The pre-CPB arterial and retrograde cannula lactate levels were similar in all the groups. Arterial and retrograde cannula lactate levels after the unclamping of the aorta were higher than before CPB in all the groups (Figure 3). Compared with the other groups, the retrograde cannula lactate levels were found to be higher in the TIVA group.

The fentanyl consumption of the TIVA group was significantly higher than in the volatile anesthetic groups (TIVA 6643.82 micgr ±1184.92; Sevo group 2485.00 micgr ±184.85; Iso group 2441.25 micgr ±174.76).

Preoperative echocardiography was maintained, and the ejection fractions (EF1) were similar in the three groups. Also, postoperative echocardiography showed that the ejection fractions at the third postoperative day (EF2) were not different within the groups. On the other hand, according to the preoperative and postoperative EF change, the groups showed statistical differences (p=0.044). There was an increase in EF in the Sevo group while it decreased in the TIVA and Iso groups (Figure 4). This difference
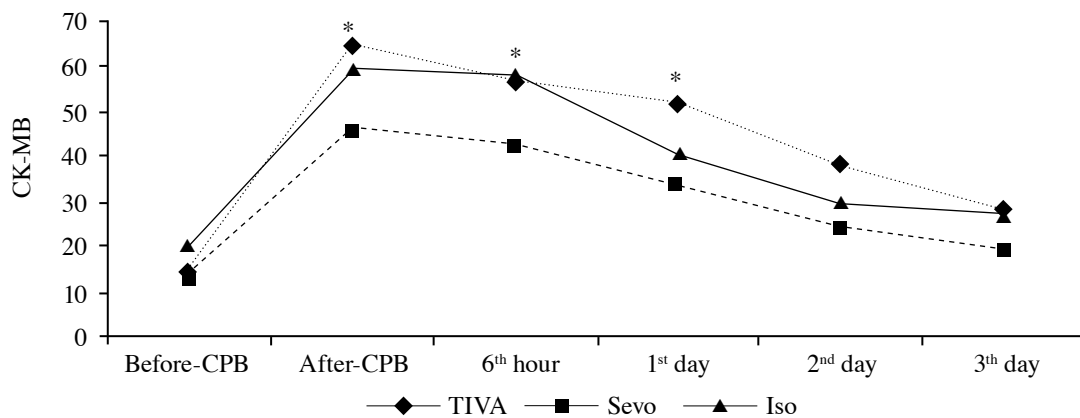

Figure 2. The change in CK-MB (as U/L). CK-MB: Creatinine kinase myocardial fraction; * p<0.001 for all groups compared to before-CPB: Before cardiopulmonary bypass; After-CPB: After cardiopulmonary bypass.
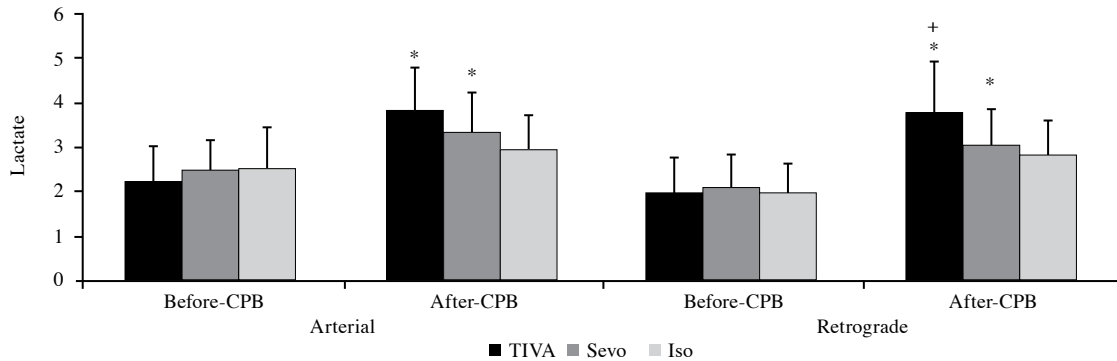
Figure 3. Lactate levels (as mg/dl). * p<0.001 as compared to before-CPB: Before cardiopulmonary bypass; After-CPB: After cardiopulmonary bypass; + p<0.05 as compared between groups.

in the Sevo group was statistically significant (p=0.003 compared with the TIVA group; p=0.001 compared with the Iso group). When preoperative and postoperative end-diastolic size and ventricular scores were evaluated, there was no difference either within the groups or between the groups. The preoperative and postoperative changes in end-diastolic size and ventricular scores were statistically similar (p=0.26; p=0.66, respectively).

The need for an inotropic agent was seen in two patients in the TIVA group, three patients in the Sevo group, and two patients in the Iso group, and there was no difference between the groups (p=0.05). Mechanical ventilation periods (MVP) were similar in the TIVA, Sevo, and Iso groups postoperatively (8.04±0.2 hours; 7.8±0.1 hours; 8.02±0.2 hours, respectively). Intensive care unit (ICU) stays were calculated and found to be similar in all the groups (14.4±0.2 hours; 13.9±0.3 hours; 14.1±0.3 hours, respectively). Hospital stays (HS) were also similar (4.9±0.1 days; 5.2±0.1 days; 5.4±0.3 days, respectively).

No patient developed a cerebrovascular event, and no hemofiltration or dialysis was indicated in the groups. Postoperatively, no death or transmural infarct was seen in the three groups.
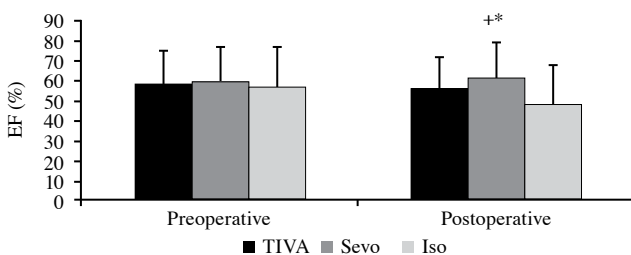

Figure 4. Ejection fraction change between groups. * p=0.003 compare to TIVA group; + p≤0.001 compared to Iso group.

DISCUSSION

This study compared the cardioprotective effects of the Sevo and Iso groups with the fentanyl-based TIVA group, and there was no difference between the groups in terms of protection. However, in the Sevo group, there was a significant increase in EF on the postoperative third day. The increments of the lactate levels following the unclamping of the aorta were less in the volatile groups when compared with the TIVA group. Although they were not statistically significant, the increases in the cTnI and CK-MB levels at the postoperative sixth hour in the Sevo group were less than in the TIVA group. Therefore, we concluded that the volatile anesthetic groups, especially the Sevo group, seemed to protect the myocardium better.

In the past, high-dose opioid anesthetics were preferred during cardiac surgery anesthesia because of their ability to provide hemodynamic stability, but the most recent studies have shown that halogenated volatile anesthetics are more effective in protecting the myocardial structure, integrity, and function.[15-17] Two of these recent studies used propofol, which is known to have no preconditioning effect, in their TIVA groups, However, in our study, opioid anesthesia (fentanyl-midazolam) was choosen for the TIVA group. Opioids have been suggested to have preconditioning effects, and several investigators have reported that morphine may protect the myocardium from ischemic injury during cardiac surgery.[6,7] Although it is frequently used clinically, the cardioprotective effect of fentanyl still remains controversial. Kato et al.[10] demonstrated that fentanyl alleviated postischemic ventricular dysfunction. Opioid receptors and KATP channels mediated this cardioprotective effect. Again, Kato et al.[12] showed that in a rat model, fentanyl limited the infarct area by the mediation of delta opioid receptors and PKC. However, Murphy et al.[6]

compared morphine and fentanyl in their clinical study and suggested that the morphine-isoflurane combination protects the myocardium better than the fentanyl-isoflurane combination against ischemia. Our study compared the protective effects of fentanyl in clinical practical doses with volatile anesthetics, and it was concluded that the volatile anesthetics seemed to be slightly more protective than the fentanyl. In addition, sevoflurane and isoflurane used after ischemia until the end of the operation were shown to have protective effects against reperfusion injury and stunning; therefore, cardiac function was improved, disarrythmias were degraded in the postoperative period, myocardial energy was saved, and the infarct size was also reported to have shrunk.[18-21] This effect may further contribute to preconditioning. For these reasons, we prefer to use sevoflurane and isoflurane until the end of the operation.

In our study, there was no difference between the groups with regard to demographic values and hemodynamic parameters. In other studies which focused on anesthetic preconditioning and ischemic preconditioning, the CO and CI were increased compared with the control groups after CPB.[15,17] In our study, although the CI and CO increased in all three groups after bypass, there were no significant differences. This may be due to using opioids in the control group instead of propofol. We performed an echocardiography preoperatively and on the postoperative third day. The variation in EF in the Sevo group was meaningful, but there were no differences between the preoperative and postoperative echocardiographic ventricular score evaluations.

Cardiac TnI levels are the most important indicator of cardiac damage. In a study by Etievent at al.[22] there was a correlation between postoperative high cTnI values and the aortic cross-clamping period. Also, cTnI values have been found to be useful in early acute myocardial infarction (MI) and postoperative MI diagnosis and for comparisons between different cardioprotective procedures. In our study, the cross-clamping period was similar between the three groups. Our results showed that even though they were statistically insignificant, the cTnI levels were lower in the volatile anesthetics groups than in the TIVA group. This insignificant difference may be due to the preconditioning effect of fentanyl. In studies in which sevoflurane and propofol were compared, the cTnI levels were lower in the sevoflurane group.[17,23] In another study, there were no differences in the volatile anesthetic groups with regard to the CK-MB and cTnI levels; however, the N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were different, and the PKC delta and epsilon translocation was shown. Therefore, the sevoflurane preconditioning effect was clinically accepted.[3]

Biochemical markers may be an indicator of early graft occlusion. There were no ECG changes in the ST segment analysis in the three groups in our study, so we did not consider graft occlusion or any other adverse effect of surgery.

Myocardial lactate secretion can be used as a marker of myocardial protection because in the case of hypoxia and ischemia, lactate is released into the blood to compensate for the ATP level in the tissue. Hence, the lactate level shows anaerobic glycolysis and gives information about the metabolic mode.[24] In this study, the arterial and retrograde cannula lactate levels after the declamping of the aorta were higher than in the period before CPB in all groups, and this elevation was higher in the TIVA group than in the volatile anesthetic groups. Lactate metabolism is affected by many factors which results in challenging results. Some other studies detected that lactate production is only related to the CPB period, but in our study, the CPB duration was not different statistically The increase in the arterial lactate level may be related to surgical stress.[25] In a study which compared off-pump and on-pump bypass, the lactate levels were higher in the on-pump group. Accordingly, the increase in the retrograde cannula lactate levels in all groups in our study may be related to CPB.[26]

Unlike in other laboratory studies, we could not find the clinically protective effect of fentanyl. We also found no distinct difference in the cardioprotective effect between the TIVA (fentanyl-based) and volatile anesthetic groups, which is in contrast to findings in other studies comparing propofol and volatile anesthetics. Fentanyl concentrations used in experimental studies is outside the clinical range. In other words, as fentanyl binds to plasma protein at a high rate (82%), the fentanyl concentrations used in clinical studies might be insufficient.[13] Otherwise, the possibility exists that there may be some difference between species. We did not test whether or not fentanyl may potentiate the effects of volatile anesthetics, but it is known that morphine and volatile anesthetics potentiate each other.[14] Moreover, we have no clinical practice which shows that only volatile anesthetics are used in cardiac surgery. The fentanyl dose was much lower in the volatile anesthetic group than in the TIVA group. Also, it has been noted that midazolam has no preconditioning effect. In a rat study, midazolam had no effect on KATP channels or ischemic myocyte survival.[27]

As a result, since all the groups have preconditioning potential, we could not find a distinctive difference between the volatile anesthetics and the fentanyl-midazolam-based TIVA group. Even if no statistical significance was shown, we can conclude that volatile anesthetics seem to be more cardioprotective than fentanyl based TIVA regimen.

Declaration of conflicting interests

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