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Comparison of the effects of total intravenous anesthesia and inhalation anesthesia on post-perfusion injury in cardiac surgery

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SUMMARY

In this study, we aimed to compare of the effects of two different anesthetic techniques (inhalation and total intravenous anesthesia) on ischemia-reperfusion injury in cases performed open-heart surgery. Fifty nine cardiopulmonary bypass patients were randomly assigned into one of three groups: Group I desflurane (n=20), Group II sevoflurane (n=20) and Group III total intravenous anesthesia (n=19) with fentanyl and midazolam. In Group I, anesthesia was established with i.v. infusion of 1-4 μg/kg/h fentanyl citrate and 1-3% desflurane, in Group II with i.v. infusion of 1-4 μg/kg/h fentanyl citrate and 1-1.5% sevoflurane, and with i.v. infusion of 0.3–12 μg/kg/min fentanyl citrate and 0.07 mg/kg/h midazolam in Group III. Arterial blood samples were taken in the preoperative period (S_0), and at the 2nd (S_1) and 24th hours (S_2) postoperatively, and IL-6, IL-8, TNF-α, AST, ALT, CK-MB and cTnI levels were measured. In all groups, we observed similar rises in serum CK-MB, in cTnI and AST, the marker of myocardial cell injury, in ALT values, the marker of splanchnic circulation, and the levels of proinflammatory cytokines TNF-α, IL-6 and IL-8 at the postoperative 2nd and 24th hours compared with preoperative levels ($p<0.001$). In our particular experience there is no difference between inhalation and total intravenous anesthesia in the prevention of ischemic-reperfusion injury occurring during cardiopulmonary bypass and in the establishment of pharmacological preconditioning.

Key words: *Desflurane, fentanyl, reperfusion injury, sevoflurane*

ÖZET

Kalp cerrahisinde postperfüzyon hasarı üzerine total intravenöz anestezi ve inhalasyon anestezisinin etkilerinin karşılaştırılması

Bu çalışmada, açık kalp cerrahisi uygulanan olgularda iki farklı anestezi tekniğinin (inhalasyon ve total intravenöz anestezi) iskemi-reperfüzyon hasarı üzerine etkilerinin karşılaştırılması amaçlandı. Elli dokuz kardiyopulmoner bypass hastası randomize olarak 3 gruba ayrıldı: Grup I (n=20) desfluran, Grup II sevofluran (n=20) ve Grup III total fentanil ve midazolam uygulanan intravenöz anestezi grubu (n=19). Grup I'de 1-4 μg/kg/saat fentanil sitrat i.v. infüzyonu ve %1-3 desfluran, Grup II'de 1-4 μg/kg/saat fentanil sitrat i.v. infüzyonu ve %1-1.5 sevofluran, Grup III'de ise 0.3-12 μg/kg/dk fentanil sitrat ve 0.07 μg/kg/saat midazolam i.v. infüzyonu ile anestezi idamesi sağlandı. Preoperatif (S_0) dönemde, postoperatif 2. (S_1) ve 24. (S_2) saatlerde arteriyel kan örnekleri alındı ve IL-6, IL-8, TNF-α, AST, ALT, CK-MB ve cTnI düzeyleri ölçüldü. Tüm gruplarda, preoperatif değerlerle karşılaştırıldığında postoperatif 2. ve 24. saatlerde serum CK-MB, miyokard hücre hasarının göstergeleri olan cTnI ve AST, splanknik dolaşımın göstergesi olan ALT düzeyleri ve proinflamatuvar sitokinler TNF-α, IL-6 ve IL-8 değerlerinde benzer artışlar saptadık. Bu çalışmadaki deneyimimize göre kardiyopulmoner bypass esnasında oluşan iskemik-reperfüzyon hasarını önlemede ve farmakolojik önkoşullandırma oluşturmada, inhalasyon ajanları ve total intravenöz anestezi arasında herhangi bir farklılık olmadığı kanısına varılmıştır.

Anahtar kelimeler: *Desfluran, fentanil, reperfüzyon hasarı, sevofluran*

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Introduction

The basic objective in open heart surgery is to protect the myocardium against ischemia-reperfusion injury. Various clinical and pharmacological methods to protect the myocardium against ischemia-reperfusion injury and reduce surgical mortality and morbidity have been implemented over the last decade.

Ischemia leads to cellular and ultrastructural changes in the myocardium, as a result of the secretion of proinflammatory cytokines, such as TNF-α, IL-1, IL-6 and IL-8 (1).

In addition to preoperative factors (ischemic heart disease, diabetes, left ventricle dysfunction) and perioperative agents (such as low cardiac output syndrome and splanchnic hypoperfusion), anesthetic techniques (inhalation anesthesia and total intravenous anesthesia [TIVA]), blood transfusion and postoperative measures also lead to changes in the secretion of proinflammatory cytokines (1-3).

We investigated the effects of inhalation (desflurane and sevoflurane) anesthesia and TIVA administered with high-dose fentanyl citrate on enzymes (CK-MB, cTnI, AST, ALT) and cytokines (IL-6, IL-8, TNF-α) that are markers of myocardial injury in the cases of open heart surgery. Our aim was to compare the effects of two different anesthetic techniques administered in open heart surgery on myocardial protection.

Material and Methods

This clinical study included 59 patients who underwent open heart surgery between January 2004 and May 2004. Approval from the local ethics committee was obtained. The cases enrolled in the study were randomly divided into three groups; Group I (n=20, desflurane), Group II (n=20, sevoflurane) and Group III (n=19), administered TIVA (TIVA; fentanyl and midazolam). Groups I and II were described as the inhalation group, and Group III as the TIVA group. Cases with neurological, endocrine (diabetic) or re-

nal pathologies (creatinine >2 mg/dL) were excluded from the study. Cases re-operated during the postoperative period were removed from the study. Cases were premedicated 30 minutes prior to the surgery with 5 mg diazepam (i.m.).

For the induction of anesthesia, all cases were given 2 mg/kg propofol (Propofol®, Fresenius Kabi GmbH, Deutschland) and 10-25 µg/kg fentanyl citrate (Fentanyl Citrate®, Abbott Laboratories), and intubation was performed by establishing muscle relaxation with 0.1 mg/kg vecuronium (Norcuron®, N.V. Organon). In Group I, anesthesia was administered with i.v. infusion of 1-4 µg/kg/h fentanyl citrate and end-tidal 1-3% desflurane (Suprane®, Eczacıbaşı-Baxter) in a 60/40% O_2/air mixture. In Group II anesthesia was established with i.v. infusion of 1-4 µg/kg/h fentanyl citrate and end-tidal 1-1.5% sevoflurane (Sevorane®, Abbott Laboratories) in a 60/40% O_2/air mixture. In Group III anesthesia was administered with an i.v. infusion of 0.3–12 µg/kg/h fentanyl citrate and i.v. infusion of 0.07 mg/kg/h midazolam (Dormicum®, Roche İlaç Sanayi Laboratories). Following induction, cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) measurements were taken and recorded pre-pump (T_0), and at the 10th (T_1) and 20th (T_2) minutes after pump extraction by inserting the probe of a non-invasive cardiac output device into the endotracheal tube (NICO 7300, Novametrix Medical Systems Inc. Wallingford, USA).

Body temperature was monitored using a temperature probe inserted in the bladder (Hewlett Packard Viridia). Moderate hypothermia (28-32 °C) was applied during pumping. Anticoagulation was provided with 300 IU/kg heparin (Nevparin®, Mustafa Nevzat İlaç Sanayi) 5 minutes before CBP was commenced. Additional doses of heparin were administered when necessary in order to provide "activated clotting time" (ACT) levels above 450 seconds.

The same make of perfusion pump (Stockert, SHRP 1010), membrane oxygenator and circulation lines were used for all patients. To the initial solution was added 20 mL/kg 0.9% NaCl (Mediflex®, Eczacıbaşı Baxter), 1.5 mL/kg 20% mannitol (Mannitol®, Eczacıbaşı Baxter), 8 mg dexamethasone (Deksamet®, Biosel İlaç Sanayi) and 30 mEq $NaHCO_3$ (Sodyum Bikarbonat®, Galen İlaç Sanayi). Perfusion strategy was regulated in such a way as to establish an average arterial pressure of 60-80 mmHg, and a flow of 2.4 L/dk/m^2. For myocardial protection, 10-12 mL/kg St. Thomas II cardioplegic solution (Plejisol®, Abbott Laboratories) containing 16 mEq/L potassium and brought to neutral pH with the addition of 20 mEq bicarbonate per litre was administered at +4 °C through the aortic root at a pressure of 80-100 mmHg. Simultaneously, serum physiologic at +4 °C and topical cooling were administered. Immediately before the aortic clamp was opened, terminal warm blood at +36 °C was given as an antegrade (5 mL/kg).

Three 10-ml arterial blood samples were taken from patients for the measurement of IL-6, IL-8 and TNF-α levels in the preoperative period (S_0), and at the 2nd (S1) and 24th hours, postoperatively (S_2). A 5 ml amount of one sample, and 5 ml at -80 °C were recorded by measuring AST, ALT, CK-MB and cTnI values. IL-6 (Biosource IL-6 Easia kit, Kac1261:96, Biosource Europe S.A., Rue de l'Industrie, 8 B-1400 Nivelles, Belgium), IL-8 (Biosource IL-8 Easia kit Kac1301, Biosource Europe S.A., Rue de l'Industrie, 8 B-1400 Nivelles, Belgium) and TNF-α (Biosource TNF-α Easia kit Kac1301, Biosource Europe S.A., Rue de l'Industrie, 8 B-1400 Nivelles, Belgium) levels were measured using the "Elisa" technique with measuring devices (Medispec ESW 300, Elisa Plate Washer, Model: 2067, Awareness Technology Inc., Palm City, FL, USA and Medispec ESW 200 Elisa Plate Reader, Model: 2106, Awareness Technology Inc., Palm City, FL, USA) at the Department of Biochemistry and Clinical Biochemistry of GATA Haydarpasa Training Hospital.

SPSS for Windows 10.0 was used for statistical analysis. One-way ANOVA and Tukey's HSD test were used in the comparison of quantitative data demonstrating normal distribution patterns between groups, and intergroup comparisons were performed using the paired sample test. Parameters not exhibiting normal distribution were analyzed using the Kruskall Wallis and Mann Whitney U tests, while intergroup comparisons were conducted using the Wilcoxon signed ranks test. $p<0.05$ with a confidence interval of 95% was regarded as significant.

Results

When the demographic characteristics of the cases, pre-operative characteristics and surgery details were compared in the study groups, there were no statistically significant differences among the groups ($p>0.05$) (Tables I and II).

When pre-operative characteristics of the cases were compared, no significant differences were determined in ejection fraction, body surface area and the

Table I. Demographic characteristics of the groups

	*Group I (n=20)**	*Group II (n=20)**	*Group III (n=19)**
Age (year)	57.40±17.66	54.95±18.62	57.05±14.09
Sex (F/M)	4/16	5/15	5/14

*: Values are given as mean±standard deviation

Table II. Distribution of the pre-operative characteristics of the groups

		Group I (n=20)	Group II (n=20)	Group III (n=19)
Ejection fraction (%)*,¶		52.00±6.76	52.00±7.50	54.47±6.43
Body surface area (m^2)*		1.75±0.18	1.74±0.14	1.78±0.18
Hypertension	Yes	12	13	12
	No	8	7	7

*: Values are given as mean±standard deviation
¶: Ejection fraction exhibits no significant differences among the groups with respect to body surface area and hypertension (p>0.05)

presence of hypertension and duration of surgery, and cross-clamp among the groups (p>0.05).

Biochemical parameters in the study groups are shown in Table III. Measurements taken at S_0, S_1 and S_2 revealed no significant differences among the groups in terms of AST, ALT, CK-MB or cTnl values (p>0.05). Statistically significant increases were determined in AST, ALT, CK-MB and cTnl measurements in Groups I, II and III over the periods S_0-S_1 and S_1–S_2 (p<0.001).

Table III. Analysis of the biochemical parameters of the groups

		Group I (n=20)	Group II (n=20)	Group III (n=19)
AST (U/L)*	S0	26.50±10.67	23.50±8.35	24.00±8.66
	S1	60.65±23.47**	56.10±2.33**	47.63±12.57**
	S2	66.05±24.79**	70.20±34.76**	59.21±13.26**
ALT (U/L)*	S0	37.95±21.96	33.40±16.05	34.05±16.43
	S1	71.75±36.64**	60.20±26.35**	50.84±17.48**
	S2	67.30±35.66**	70.00±28.10**	57.57±23.12**
CK-MB (U/L)*	S0	2.15±2.54	1.27±1.17	1.21±0.96
	S1	38.20±33.14**	60.05±46.91**	45.49±28.90**
	S2	36.20±59.68**	33.41±38.05**	20.56±17.84**
CTnl (ng/mL)*	S0	0.11± 0.36	0.004±0.13	0.11±0.43
	S1	3.64±3.87**	4.47±3.72**	3.55±2.48**
	S2	3.08±1.91**	4.43±5.72**	2.18±1.86**

*: Values are given as mean±standard deviation
**: p<0.001 highly significant according to intra-group base values

Table IV. Analysis of the cytokine measurements of the groups

		Group I (n=20)	Group II (n=20)	Group III (n=19)
IL-6 (pg/mL)*	S0	2.22±2.10	1.89±2.81	3.08±2.11
	S1	358.9±194.8**	287.1±145.6**	352.7±142.9**
	S2	167.6±60.2**	150.0±67.1**	159.4±59.0**
IL-8 (pg/mL)*	S0	5.12±1.38	5.02±1.17	5.02±1.04
	S1	64.62±12.35**	37.13±11.20**	71.06±5.79**
	S2	32.51±10.04**	32.78±10.06**	30.08±3.43**
TNF-α (pg/mL)*	S0	3.04±0.63	2.91±0.64	2.96±0.63
	S1	9.56±1.57**	9.35±1.85**	9.23±1.61**
	S2	7.16±0.96**	7.21±1.31**	6.63±0.79**

*: Values are given as mean±standard deviation
**: Highly significant according to the intra-group base values (p<0.001)

The proinflammatory cytokine levels of the cases in the study groups are shown in Table IV. In inter-group comparisons of IL-6, IL-8 and TNF-α measurements from blood samples taken at S_1, IL-6 and IL-8 increases in Group II were significantly lower than those of the other groups (p<0.05), but samples taken at S_2 revealed no statistically significant differences (p>0.05). A statistically significant difference was detected in IL-6, IL-8 and TNF-α between timings (S_0-S_1) and (S_1–S_2) in Groups I, II and III (p<0.001).

Discussion

Myocardial reperfusion injury is the most common cause of morbidity seen in the postoperative period in open heart surgery. The most important agent in the occurrence of reperfusion injury is systemic inflammation (1). The other systemic diseases of the patient, preoperative cardiac function, the surgical procedures applied, methods of heart protection, whether blood flow during CPB is pulsatile or non-pulsatile, temperature during CPB, the pump type employed, oxygenator and membrane type and pharmacological agents used before or during reperfusion are the factors all affecting reperfusion injury (2,4).

Humoral immunity and cellular immunity are known to rise and decline, respectively with increasing age (5,6). Roth-Isigkeit et al. have divided cases performed coronary artery bypass greft (CABG) into two groups on the basis of age (group 1 <50 and group 2 >65 years of age), and investigated whether there was a post-CPB difference in IL-6, IL-10 and TNF-α secretion, and determined no statistically significant differences between cytokine levels in the two groups (6). In agreement with this finding, no statistically significant differences were determined in terms of cytokine levels in cases of different ages subjected to open heart surgery (p>0.05).

Factors such as blood contact with extracorporeal foreign surface and blood injury as it passes through the pump and oxygenator reflect the systemic inflammatory response arising during CPB (2).

Sheeran and Hall reported that extracorporeal flow during cardiac surgery triggered inflammatory response and one of the most important stimuli for leukocyte activation and production was the blood being exposed to artificial extracorporeal circuits (7). Wei et al. divided patients of CABG surgery into two groups, the first being operated on with CBP, the other with off-pump (8). Post-pump cytokine release at different times was then investigated (IL-6, IL-8 and TNF-α). These authors determined that TNF-α and

IL-6 levels rose significantly in both groups, while IL-8 levels rose less significantly in the off-pump group compared to the CPB group ($p<0.05$). Strüber et al. also divided patients of CABG surgery into two groups; CBP and minimal invasive direct coronary artery by-pass (9). They investigated postoperative IL-6, IL-8 and TNF receptor 1 and 2 levels and concluded that these were higher in the CBP group. All the cases in our study were operated on CBP. When we examined post-pump cytokine levels we determined that these rose in agreement with that in the CBP group in other studies.

Protection of the myocardium against temporary ischemia occurring in the heart during CBP is essential. In addition to general body and regional hypothermia, the chemical reduction of myocardial cell metabolism with cardioplegics is another essential element of this protection. Whether cardioplegic agents are crystalloid or colloid and whether these are given as retrograde or antegrade are factors preventing inflammatory response, and thus reperfusion injury (2).

In addition to the application of general body and regional hypothermia methods, we established cardiac arrest with cold crystalloid cardioplegia and ensured protection of the myocardium by giving cold blood cardioplegia as an antegrade at 20-minute intervals. We determined a post-pump rise in cTn1 levels in all cases ($p<0.001$). Despite the application of general body and regional hypothermia during CBP, we think that the myocardium can be affected by environmental temperature, for which reason post-pump myocardial injury will decline with improved maintenance of the hypothermia applied.

In addition to intraoperative hemodynamic parameters, postoperatively increased biochemical enzymes (CK-MB, cTnI, cTnT, CK and myoglobin) and cytokines (IL-6, IL-8, IL-1, IL-10 and TNF-α) are known to be important markers of the level of post-cardiac surgery reperfusion injury.

Hazar et al. investigated post-cross clamp CK, CK-MB and cTnI in the cases of open heart surgery and suggested that cTnI could be a more specific marker of cardiac injury compared to other enzymes (10). Song et al. investigated post-CBP CK-MB and cTnI levels in patients of CABG surgery and determined a statistically significant increase in these values compared to pre-pump levels (11). In agreement with other studies, we also determined that CK-MB and cTnI levels in the pre-operative period rose in a statistically highly significant manner on leaving the pump ($p<0.001$).

Following cardiovascular surgery, temporary and medium-severity impairment in liver and kidney functions related to splanchnic and renal blood flow changes are known to be more frequent and to have a direct effect upon morbidity. But et al. evaluated postoperative liver and kidney function tests in cases administered inhalation anesthesia (desflurane-fentanyl) and TIVA (midazolam-fentanyl) (12). They determined a statistically significant rise in ALT, GGT, creatinine and BUN levels in both groups enrolled in their study. This was greater in the desflurane group compared to the TIVA group. In our study we evaluated AST and ALT levels, and those CK-MB and cTnI, sensitive biochemical parameters of ischemia-reperfusion industry. In agreement with the literature, we determined that measurements taken at the 2nd (S1) and 24th (S2) hours post-pump exhibited a statistically significant increase compared to pre-operative levels (S_0) ($p<0.001$).

We evaluated the protective effect on the myocardium against ischemia-reperfusion injury of desflurane, one of the modern inhalation anesthetics, with biochemical parameters (CK-MB, cTnI, AST, ALT) and proinflammatory cytokine (IL-6, IL-8 and TNF-α) measurements. In agreement with the literature, compared with pre-pump values, we determined that desflurane had similar effects on biochemical parameters and proinflammatory cytokine levels in measurements taken at hours 2 and 24.

Several experimental and clinical studies have shown that sevoflurane has cardioprotective effects against ischemia-reperfusion injury (13-16). Zaugg et al. showed that the protective effect on the myocardium against ischemia-reperfusion injury of sevoflurane is by way of, as in desflurane, the main mitochondrial K_{ATP} channels (13). Nader et al. randomly assigned 21 cases administered TIVA anesthesia into two groups, 11 patients being given sevoflurane during pumping (14). They determined that in cases given sevoflurane the levels of β-integrin, IL-6 and TNF-α released as an inflammatory response to ischemia-reperfusion injury were significantly lower. Azap et al. investigated the effect of sevoflurane and TIVA in CABG surgery on the proinflammatory cytokines IL-6, IL-8 and TNF-α and determined that IL-6 levels were higher in the pre-pump sevoflurane group compared to the other groups (17). In addition, they established that there was a correlation between the release of IL-6, IL-8 and TNF-α and the timing of aortic cross-clamp. Azap et al. looked at serum AST, ALT, GGT, CRK, BUN and LDH levels in the pre- and post-operative periods (on days 1 and 5 and week 6) in cases administered CABG in order to investigate the effects of sevoflurane and TIVA on liver and kidney functions (18). They demonstrated a temporary impairment of liver and kidney functions after sevoflurane anesthesia, but this

impairment was more closely correlated to surgical technique than method of anesthesia provision.

The serum AST and ALT levels measured in the analysis of splanchnic perfusion in 20 cases given sevoflurane anesthesia for the purpose of protecting the myocardium against ischemia-reperfusion injury were in agreement with the results of the study by Azap et al. (18). We also determined similar temporary increases in liver function tests after sevoflurane anesthesia in cases undergoing open heart surgery.

Azap et al. also detected a correlation between IL-6, IL-8 and TNF-α release and aortic cross-clamp duration (17). We also determined that IL-6, IL-8 and TNF-α levels exhibited a statistically significant rise in the 2nd and 24th hours post-pump compared to their preoperative values ($p<0.001$), and that all cytokine levels reached their highest values in measurements taken at the 2nd hour.

We conclude with these findings that neither inhalation nor TIVA anesthesia is superior to the other in the prevention of ischemia-reperfusion injury and the establishment of pharmacological preconditioning. We consider that anesthetic method by itself is insufficient in preventing or reducing ischemic-reperfusion injury to minimum. However short pump, aortic cross-clamp-duration and the knowledge and experience of the surgeon and anesthetist are also of great importance.

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