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Comparative Study between Sevoflurane and Isoflurane on Myocardial Protection Open Heart Surgery

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Abstract

Background: Numerous mechanisms for myocardial protection associated with volatile anaesthetic administration have been proposed. However, research on the effects of sevoflurane and isoflurane on myocardial protection yielded contradictory results.

Aim of Study: The purpose of this study is to compare the myocardial protective effects of sevoflurane and isoflurane in CABG surgery.

Patients and Methods: This prospective randomized clinical double blind study included 106 patients, selected from the attendees of Al-Azhar University Hospitals during the period between December 2021 till June 2022. The study protocol was approved by the Local Ethics Committee and written informed consents were obtained individually. A sample of 106 patients were randomly allocated in equal numbers to receive either sevoflurane or isoflurane. We evaluated the patient demographic and baseline characteristics, including age, sex, body mass index (BMI), American Society of Anaesthesiology (ASA) physical status, Ejection Fraction, and the preoperative medications. Heart rate (HR), systolic, mean and diastolic arterial pressures (SAP, MAP, DAP) readings were recorded at different time points. In addition, Troponin-T, creatine kinase (CK), and CK-MB were measured in all blood samples before induction of anesthesia, after aortic unclamping, 12 and 24 hours postoperatively. Echocardiograph for all patienta 24h postoperative to evaluate the myocardial function.

Results: No significant difference was reported between both groups regarding the demographic characteristics. Baseline Heart rate was comparable between the two study groups with no statistically significant difference. Heart rate recordings showed more stability in the sevofluran group. Troponin-T, CK and CK-MB were investigated prior to the surgery, after removal of the cross-clamping, 12 and 24 hours postoperatively. The three cardiac enzymes showed comparable efficacy at baseline, with non-significant results. After declamping, Troponin-T, CK and CK-MB increased in both groups, but higher recordings were significantly reported in the isofluran group.

Conclusion: During CABG surgery, sevoflurane has a greater cardioprotective effect than isoflurane. When compared to isoflurane, sevoflurane was associated with greater stability and fewer variations from baseline. The better myocardial protection associated with sevoflurane is inferred by the lower levels of the myocardial injury markers troponin-T, CK, and CK-MB, observed with sevoflurane, compared to isoflurane. Further high quality studies are needed to determine the potential impact of the volatile anaesthetic regimen selection on long-term cardiac function after CABG surgery.

Key Words: *Isoflurane – Sevoflurane – Preconditioning – Myocardial protection – CABG.*

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Introduction

IT has been repeatedly reported that coronary artery bypass graft (CABG) surgery contributes to myocardial dysfunction and is associated with significant morbidity and mortality. Indeed, the efficacy of myocardial preservation will reduce the consequences of ischemia/reperfusion injury as well as the length of in-hospital stay **[1]**. Many methods for myocardial protection have been proposed, including systemic hypothermia, topical hypothermia, and cardioplegic techniques **[2]**.

Interestingly, there is compelling evidence from experimental and in-vivo studies that volatile anaesthetics have protective effects against ischemia-reperfusion injury that are independent of their hemodynamic effects **[3]**. Despite numerous studies, the mechanism of action of volatile anaesthetic agents in terms of myocardial protection remains unknown. Nonetheless, numerous mechanisms for myocardial protection associated with volatile anaesthetic administration have been proposed **[4]**. Volatile anaesthetic agents have been shown to improve cardiac function and reduce the frequency of revascularization rhythm disturbances when administered prior to and after ischemia. This property has been linked to the preconditioning effect of anaesthetics; nevertheless, volatile anaes-

thetics have been reported to provide protection even when administered only during the revascularization period. Volatile anaesthetic agents have the potential to provide myocardial protection through anaesthetic preconditioning, as well as renal and cerebral protection [5]. When administered after myocardial ischemia, volatile anaesthetics have been shown to protect against reperfusion injury [6]. However, research on the effects of sevoflurane and isoflurane on myocardial protection yielded contradictory results. The purpose of this study is to compare the myocardial protective effects (as measured by the investigated enzyme profile) of sevoflurane and isoflurane administered to patients chosen for coronary artery bypass graft (CABG) surgery over the course of the procedure, including the hypothermic cardioplegia period.

Patients and Methods

Study design and sampling: This prospective randomized clinical double blind study included 106 patients, selected from the attendees of Al-Azhar University Hospitals. The study protocol was approved by the Local Ethics Committee and written informed consents were obtained individually. Sample size was calculated according to the formula Sample size (n)=p(1-p) x (Zα)2 ÷ (ME)2, in which the proportion of suspected myocardial protection (p)=0.5, Confidence level=0.95, Zα 2 sided=1.96, Marginal error (ME)=0.1, and the expected drop out rate (f)=10%. A sample of 106 patients were randomly allocated in equal numbers to receive either sevofluran or isofluran, using computer-generated random numbers placed in separate opaque envelopes.

Anesthetic technique: All patients were premedicated with morphine 0.1mg/kg IM 30 minutes before surgery. Radial artery catheter were placed under local anesthesia prior to induction. Induction of general anesthesia was done with fentanyl 3µg/kg followed by propofol 1-2mg/kg. Endotracheal intubation was facilitated by rocuronium 0.8mg/kg. Intermittent positive pressure ventilation was performed to maintain an end-tidal co2 between 35-45mmHg. In the sevoflurane group, anesthesia was maintained by inhaled sevoflurane at 1 (minimum alveolar concentration) MAC in oxygen:air (FiO2 50%) and in the isoflurane group, inhaled isoflurane at 1 MAC in oxygen: air (FiO2 50%) was applied. The depth of anesthesia before, during and after cardiopulmonary bypass will be monitored by bispectral index and will be controlled by adjusting the dose of inhalational anesthetic. Sevoflurane did not exceed 4% and isoflurane did not exceed 2.5% MAC. Cardiopulmonary bypass was performed using a membrane oxygenator, hemodilution and moderate systemic hypothermia (28-32°C). Multidose cold crystalloid cardioplegia with potassium (20mEq/l) and topical saline ice flush were used for myocardial protection during bypass in both groups. During extracorporeal circulation, all patients in both groups received total intravenous anesthesia. All patients were maintained maintained with a propfol infusion (5-6mg/kg/h) and fentanyl infusion (3-5µ/kg/h). All medications were continued at the same dose during bypass in the cardiopulomnary machine.

Assessment: We evaluated the patient demographic and baseline characteristics, including age, sex, BMI, ASA physical status, Ejection Fraction, and the preoperative medications. Heart rate (HR), systolic, mean and diastolic arterial pressures (SAP, MAP, DAP) readings were recorded just prior to induction (T1), post induction (T2), post intubation (T3), post skin incision (T4), post sternotomy (T5), after the removal of the cross-clamp (T6), at the 10^{th} minute (T7) and at the 20^{th} minute following completion of the extracorporeal circulation (T8), at the 1^{st} hour (T9), at the 6^{th} hour (T10), at the 12^{th} hour (T 11), and at the 24^{th} hour (T 12) after ICU admission. In addition, Troponin-T, creatine kinase (CK), and CK-MB were measured in all blood samples before induction of anesthesia, after aortic unclamping, 12 and 24 hours postoperatively. Echocardiograph for all patienta 24h postoperative to evaluate the myocardial function.

Statistical analysis: Data will be processed using the SPSS for Windows version 13.0 program (Chicago, IL, USA). Continuous variables will be presented as mean ± standard deviation and median (minimum-maximum) values. Intergroup and intragroup comparisons were accomplished using *t*-test, Chi-square test, Mann-Whitney test and two-way analysis of variance. A sample size of 20 patients per group are needed for comparison between two groups (α=0.05, two samples *t*-test and power of the study of 85%). The statistically significant value will be assumed to be $p<0.05$.

Results

The present study was conducted on 106 patients, randomly assigned into two equal groups; sevofluran and isofluran groups, 53 patients in each group. No significant difference was reported between both groups regarding age, sex, BMI, EF%, pump duration, cross-clamping duration, ASA physical status and the preoperative medications (Table 1).

Table (1): Comparison between both groups according to the baseline and demographic characteristics.

Demographic data	Sevoflurane (n=53)	Isoflurane (n=53)	*p*-value
Age (years)	53.5±8.46	52.28±7.61	0.061
Sex n (%):			
Male	22 (41)	25 (47)	0.538
Female	31 (59)	28 (53)	
BMI (kg/m^2)	23.3±2.67	24.8±2.57	0.679
ASA physical status n (%):			
ASA 3	43 (81)	41 (77)	0.278
ASA 2	10 (19)	12 (23)	
Pump duration	83.8±13	79.2±9.5	0.471
Cross-clamping duration	53.8±2.5	51.3±1.9	0.313
Number of coronary grafts	3.1±0.1	2.5±0.1	0.091
Ejection fraction (%)	63.7±8.1	65.9±9.5	0.116
Perioperative medication n (%):			
B blockers	24 (45)	21 (40)	0.63
Calcium channel blockers	18 (34)	19 (36)	
Nitrates	11 (21)	13 (24)	0.45

Using: *t*-Independent Sample *t*-test.
x^2: Chi-square test.
p-value >0.05 Ns.
Data are represented as mean ± SD, number (%).

Baseline Heart rate was comparable between the two study groups with no statistically significant difference. Heart rate recordings showed more stability in the sevofluran group. After induction, reduction of heart rate was more significantly encountered in the isofluran group, compared to the sevofluran group (68 Vs 72; p=0.001). In addition, heart rate significantly showed less variations from baseline in the sevofluran group, after intubation, skin incision and sternotomy. Indeed, the postoperative recordings were higher in the sevofluran group but the results were not significan, except at the 6th hour in ICU (p=0.031) (Table 2, Fig. 1).

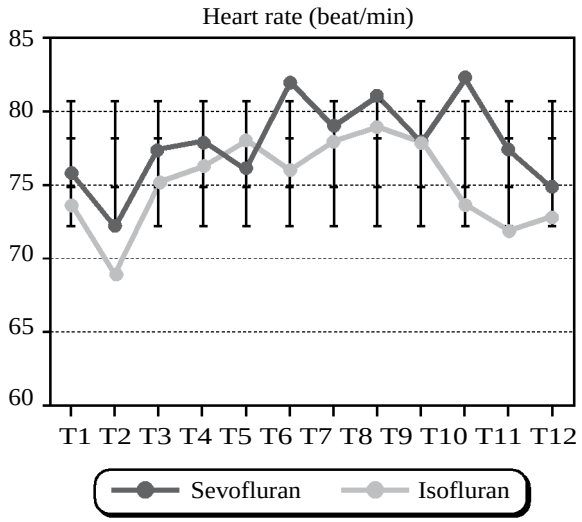

Fig. (1): Trends of the heart rate throughout the study period.

Table (2): Comparison between studied groups according to the heart rate (beat/min).

Heart rate (beat/min)	Sevoflurane (n=53)	Isoflurane (n=53)	*p*-value
T1	75.77±6.47	73.69±6.15	0.03
T2	72.30±9.38	68.97±7.91	0.001**
T3	77.54±11.67	75.20±7.28	0.024*
T4	78.06±10.93	76.37±10.38	0.031*
T5	76.15±7.43	78.06±8.63	0.015*
T6	82±9.81	76±9.74	0.113
T7	79±8.33	78±9.53	0.248
T8	81±7.63	79±8.55	0.117
T9	77.97±9.96	78.03±7.02	0.141
T10	82.23±11.27	73.67±10.14	0.031*
T11	77.43±10.13	71.94±8.38	0.272
T12	74.77±8.36	72.86±13.7	0.115

Using: *t*-Independent Sample *t*-test.
Data are represented as mean ± SD.
p-value >0.05 NS.
**p*-value <0.05 S.
***p*-value <0.001 HS.

Table (3) summarized the changes in the MAP at the different time points. There is no statistically significant difference between groups according to the mean BP (mmHg) at baseline with *p*-value (p>0.05 NS). After, intubation, skin incision, and sternotomy, patients in the isofluran group showed lower MBP recordings, compared to the control group, but this result was not significant. Indeed, the subsequent postoperative recordings were also non-significant (Table 3 & Fig. 2).

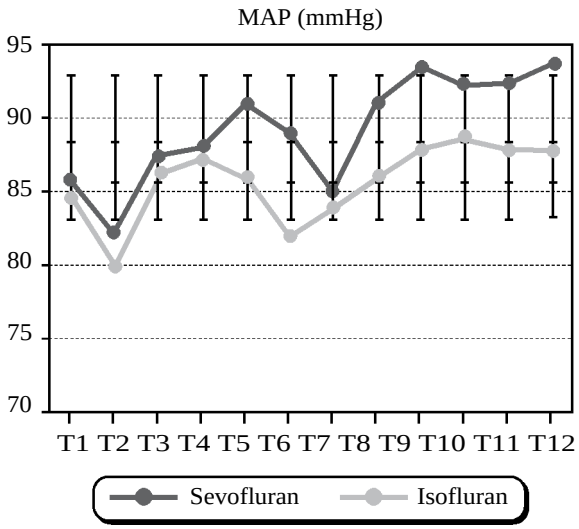

Fig. (2): Trends of mean arterial pressure values in both groups.

Table (3): Comparison between studied groups according to mean Arterial Pressure (MAP) (mmHg).

MAP (mmHg)	Sevoflurane (n=53)	Isoflurane (n=53)	*p*-value
T1	85.77±15.47	84.69±16.15	0.03
T2	82.30±16.38	79.97±14.91	0.301
T3	87.54±11.67	86.20±7.28	0.124
T4	88.06±10.93	87.37±10.38	0.531
T5	91.15±7.43	86.06±8.63	0.061
T6	89±16.81	82±13.74	0.113
T7	85±8.33	84±9.53	0.248
T8	91±17.63	86±14.55	0.117
T9	93.51±18.96	87.93±14.2	0.141
T10	92.23±18.27	88.67±13.14	0.081
T11	92.43±18.13	87.94±14.38	0.272
T12	93.77±18.36	87.86±13.7	0.115

Using: *t*-Independent Sample *t*-test.
Data are represented as mean ± SD.
p-value >0.05 NS.

Similarly, the systolic and diastolic arterial pressures (SAP & DAP) showed less reduction from the baseline values in the sevofluran group after induction of anesthesia. After intubation, skin incision, and sternotomy, the SAP and DAP were higher in the sevofluran group, compared to the isofluran group. SAP and DAP showed less variations from the baseline in the sevofluran group but all the comparisons were not significant (Tables 4,5).

Table (4): Comparison between studied groups according to Systolic Arterial Pressure (SAP) (mmHg).

SAP (mmHg)	Sevoflurane (n=53)	Isoflurane (n=53)	*p*-value
T1	122.37±11.17	125.14±10.24	0.113
T2	118.51±13.21	111.85±13.11	0.421
T3	123.51±14.27	119.32±11.28	0.084
T4	129.55±12.13	125.47±16.11	0.391
T5	127.72±9.25	126.21±15.81	0.611
T6	125±14.81	121±9.88	0.813
T7	123±10.33	115±11.74	0.098
T8	125±14.63	117±11.18	0.075
T9	122.22±11.84	126.75±11.23	0.170
T10	128.11±15.39	126.18±15.03	0.115
T11	125.54±11.13	122.53±11.68	0.301
T12	121.54±12.15	118.44±15.76	0.091

Using: *t*-Independent Sample *t*-test.
Data are represented as mean ± SD.
p-value >0.05 NS.

Table (5): Comparison between studied groups according to Diastolic Arterial Pressure (DAP) (mmHg).

DAP (mmHg)	Sevoflurane (n=53)	Isoflurane (n=53)	*p*-value
T1	66.47±11.17	64.55±10.24	0.113
T2	64.51±13.21	63.95±13.11	0.421
T3	69.75±14.27	69.65±11.28	0.084
T4	67.25±12.13	68.35±16.11	0.391
T5	72.65±9.25	66.05±15.81	0.611
T6	71±14.81	62.5±9.88	0.813
T7	66±11.13	68.5±9.62	0.178
T8	72.5±9.63	70.5±11.52	0.305
T9	74.22±10.84	68.51±10.15	0.075
T10	74.41±8.39	69.95±9.13	0.415
T11	75.68±11.35	70.53±9.88	0.281
T12	75.07±10.18	72.54±11.66	0.129

Using: *t*-Independent Sample *t*-test.
Data are represented as mean ± SD.
p-value >0.05 NS.

Moreover, Troponin-T, CK and CK-MB were investigated prior to the surgery, after removal of the cross-clamping, 12 and 24 hours postoperatively. The three cardiac enzymes showed comparable efficacy at baseline, with non-significant results. After declamping, Troponin-T, CK and CK-MB increased in both groups, but higher recordings were significantly reported in the isofluran group. Similarly, the cardiac enzymes continued to rise more prominently in the isofluran group, at 6 and 12 hours post ICU admission ($p<0.001$) (Table 6) (Figs. 3,4,5).

Table (6): Comparison between studied groups according to Troponin T, CK and CK-MB.

Variables	Sevoflurane (n=53)	Isoflurane (n=53)	*p*-value
Troponin T (ng/ml):			
T1	0.60±0.55	0.57±0.42	0.421
T6	1.15±0.85	1.63±0.35	0.001**
T11	4.25±0.63	6.31±0.43	0.001**
T12	5.64±0.85	8.31±1.25	0.001**
CK (IU/l):			
T1	91.25±7.44	96.15±9.12	0.116
T6	153.10±8.22	231.2±11.52	<0.001**
T11	271.22±5.84	483.51±7.15	<0.001**
T12	432.85±8.39	718.19±5.13	<0.001**
CK-MB (IU/l):			
T1	25.75±2.44	26.15±3.12	0.311
T6	46.25±2.44	57.15±2.12	<0.001**
T11	91.25±3.44	106.15±3.12	<0.001**
T12	108.07±3.18	148.54±4.66	<0.001**

Using: *t*-Independent Sample *t*-test.
Data are represented as mean ± SD.
p-value >0.05 NS. ***p*-value <0.001 HS.

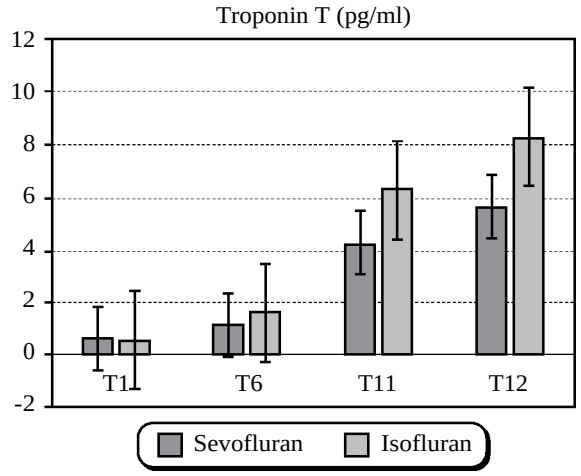

Fig. (3): Comparison of Troponin T in both groups.

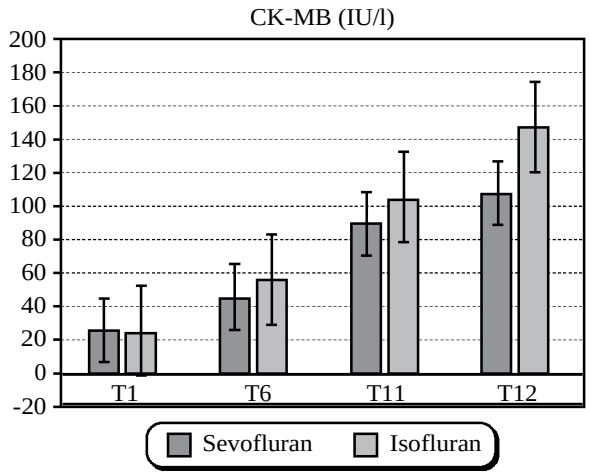

Fig. (4): Cardiac enzyme CK-MB (IU/l) distribution in both groups.

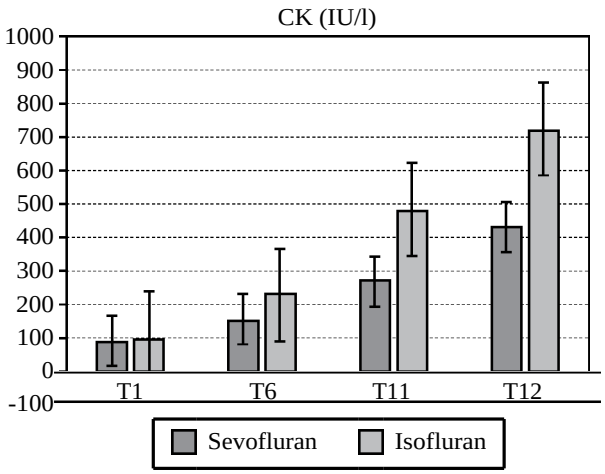

Fig. (5): Cardiac enzyme CK-MB (IU/l) distribution in both groups.

Discussion

Troponin-T, CK, and CK-MB levels were significantly lower in the sevoflurane group compared to the isoflurane group after de-clamping, 12 and 24 hours postoperatively. Furthermore, after intubation, skin incision, and sternotomy, the sevoflurane group's heart rate, systolic and diastolic blood pressure showed more stability and less variation. Following recordings revealed similar results, with no significant difference between the two groups. In the anaesthetic management of patients undergoing bypass surgery, sevoflurane has been shown to have greater cardioprotective activity. Indeed, increased troponin levels postoperatively have been shown to strongly correlate with a poor clinical outcome. Furthermore, after CABG surgery, postoperative troponin I correlates well with the mass of myocyte necrosis detected by serial cardiac magnetic resonance imaging (MRI) **[7]**.

The current study's findings are consistent with the findings of other studies. Ceyhan et al. **[8]** discovered that the levels of CK-MB and troponin-T in the sevoflurane group were significantly lower than in the isoflurane group through the 24th postoperative hour, and they concluded that sevoflurane provides better myocardial protection than isoflurane **[8]**. According to a meta-analysis study Li et al. **[9]**, the use of sevoflurane is associated with lower troponin I levels and a better cardioprotective effect than propofol **[9]**. Similar findings were reported by Yang et al. **[10]** & Liu et al. **[11]** 2016, who revealed that sevoflurane significantly improved cardiac output and stroke volume compared to propofol, but there was no difference in cardiac troponin I, creatine kinase-MB, and lactate dehydrogenase levels between the two groups **[10,11]**.

Sevoflurane has a better myocardial protective effect than isoflurane, which could be due to variety of factors. Isoflurane has been linked to the phenomenon of coronary steal, which involves the redistribution of blood from a poorly perfused region of the myocardium to an area that is adequately perfused, and this may imply that isoflurane is linked to a higher incidence of myocardial ischemia as a result of coronary steal, whereas sevoflurane is not linked to coronary steal. In addition, isoflurane raises the heart rate, which increases myocardial oxygen demand and can be harmful to ischemic patients undergoing cardiac surgery **[12]**. Furthermore, sevoflurane has more depressant activity on the myocardium than isoflurane, which may reduce the work performed and oxygen requirement associated with the surgical stress. It has been shown that sevoflurane has a better ischemic preconditioning effect than other volatile agents **[13]**.

In contrast to the current study's findings, Kiani et al. **[14]** compared the protective effect of isoflu-

rane-induced preconditioning (2.5 minimum alveolar concentration MAC) in patients undergoing elective CABG surgery and discovered a significant decrease in CK-MB isoenzyme levels 24 hours after surgery **[14]**. According to the findings of the Bastola et al. **[15]** study, exposing CABG patients to either Sevoflurane or Isoflurane did not result in a difference in postoperative cardiac biomarkers (CPK-MB and cTnI) at different time intervals **[15]**. Jones et al. **[16]** conducted a pragmatic randomised non-inferiority comparative effectiveness clinical trial in 464 adults who had undergone coronary artery bypass graft surgery **[16]**. They discovered that Sevoflurane is not inferior to isoflurane in terms of prolonged ICU stay and all-cause 30-day mortality.

Conclusion:

During CABG surgery, sevoflurane has a greater cardioprotective effect than isoflurane. When compared to isoflurane, sevoflurane was associated with greater stability and fewer variations from baseline. The better myocardial protection associated with sevoflurane is inferred by the lower levels of the myocardial injury markers troponin-T, CK, and CK-MB, observed with sevoflurane, compared to isoflurane. Further high quality studies are needed to determine the potential impact of the volatile anaesthetic regimen selection on long-term cardiac function after CABG surgery.

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دراسة مقارنة بين سيفوفلوران وإيزوفلورين على حماية عضلة القلب فى جراحة القلب المفتوح

خلفية الدراسة : من المعروف أن جراحات القلب المفتوح تساهم فى ضعف عضلة القلب وترتبط بارتفاع معدلات الاعتلال والوفيات. ستقلل فعالية الحفاظ على عضلة القلب من عواقب الإصابة بنقص التروية / ضخه ومدة الإقامة فى المستشفى.

الهدف من الدراسة : مقارنة التأثيرات الو قائية لعضلة القلب لسيفوفلوران وإيزوفلورين أثناء جراحات القلب المفتوح.

المرضى وطرق الدراسة :

تصميم البحث : دراسة مستقبلية قائمة على الملاحظة.

أساليب البحث : سيتم إجراء دراسة مستقبلية على ١٠٦ مريضاً سيتم اختيارهم من بين الحضور فى مستشفيات جامعة الأزهر فى الفترة ما بين ديسمبر ٢٠٢١ حتى يونيو ٢٠٢٢.

معايير الاشتمال : مرضى الجمعية الأمريكية لأطباء التخدير (ASA) من الدرجة الثانية والثالثة الذين تتراوح أعمارهم بين ٢٥-٦٥ عاماً والذين يسخضعون لجراحة القلب المفتوح.

معايير الاستبعاد : المرضى الذين لديهم تاريخ من احتشاء عضلة القلب خلال الأشهر الستة الماضية، وأولئك الذين يعانون من كسر طرد أقل من ٤٠٪، والذين يحتاجون إلى جراحة الشريان الأورطى أو الصمامات بالإضافة إلى جراحة تحويل مسار الشريان التاجى، ومرضى الذبحة الصدرية غير المستقرة، والحالات الطارئة، والمرضى الذين يعانون من ارتفاع إنزيم القلب قبل ٢٤ ساعة من الجراحة والحساسية المعروفة للأدوية المستخدمة فى الدراسة.

نتائج الدراسة : لم يتم الإبلاغ عن اختلاف كبير بين كلا المجموعتين فيما يتعلق بالخصائص الديموغرافية. كان معدل ضربات القلب الأساسى قابلاً للمقارنة بين مجموعتى الدراسة مع عدم وجود فرق معتد به إحصائياً. أظهرت تسجيلات معدل ضربات القلب مزيداً من الاستقرار فى مجموعة سيفوفلوران. تم فحص Troponin-T و CK و CK-BM قبل الجراحة، بعد إزالة التثبيت المتقاطع، ١٢ و ٢٤ ساعة بعد الجراحة. أظهرت إنزيمات القلب الثلاثة فعالية مماثلة فى الأساس، مع نتائج غير مهمة. بعد إزالة التخميد، زاد تروبونين تى، سى كى، سى كيه إم بى فى كلا المجموعتين، ولكن تم الإبلاغ عن تسجيلات أعلى بشكل ملحوظ فى مجموعج إيسوفلوران.

الاستنتاج : أثناء جراحة تحويل مسار الشريان التاجى، يكون للسيفوفلوران تأثير واقٍ للقلب أكبر من تأثير الأيزوفلورين. عند مقارنتها مع isoflurane، ارتبط سيفوفلوران باستقرار أكبر وتنوعات أقل من خط الأساس. يتم الاستدلال على حماية أفضل لعضلة القلب المرتبطة بالسيفوفلوران من خلال المستويات المنخفضة لعلامات إصابة عضلة القلب تروبونين -T و CK و CK-MB، التى لوحظت مع سيفوفلوران، مقارنة بالإيزوفلورين. هناك حاجة إلى مزيد من الدراسات عالية الجودة لتحديد التأثير المحتمل لاختيار نظام التخدير المتطاير على وظيفة القلب على المدى الطويل بعد جراحة تحويل مسار الشريان التاجى.