Clinical Investigation

A comparative study of pharmacological myocardial protection between sevoflurane and desflurane at anaesthestic doses in patients undergoing off pump coronary artery bypass grafting surgery

Address for correspondence:
Dr. Umesh Sivanna,
No. 12, 1st 'R' Block,
Rajajinagar,
Bengaluru - 560 010,
Karnataka, India.
E-mail: umeshbushi@yahoo.co.in

Umesh Sivanna, Shreedhar Joshi, Balaji Babu, AM Jagadeesh
Department of Cardiac Anaesthesiology, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, Karnataka, India

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/0019-5049.156867
Quick response code

ABSTRACT

Background and Aims: Perioperative myocardial ischaemia (PMI) is one of the known complications during off pump coronary artery bypass (OPCAB) surgeries. The length of hospital stay is considerably prolonged in patients with PMI. Myocardial protection is an area which is being widely researched currently to prevent or reduce the incidence of PMI. Over the last decade it has become clear that volatile anaesthetic agents are protective in the setting of PMI and reperfusion. Hence, we planned to study the effect of two different volatile anaesthetics as myocardial protective agents in OPCAB surgery. **Methods:** A total of 40 patients were enrolled for the study; Group A (sevoflurane, n = 20) and Group B (desflurane, n = 20). All patients had a baseline measurement of Trop-T, creatine phosphokinase-MB (CPKMB) and myocardial performance index (MPI) pre-operatively, which was repeated 4 h after the surgery. Chi-square/Fisher test was used to find the significance of the differences between the two agents. **Results:** Patients were comparable in demographic, baseline, biochemical and echo criteria. Post-operative CPKMB levels (desflurane - 30.85 ± 2.69 u/L; sevoflurane - 29.05 ± 5.26 u/L, P = 0.7) and number of Trop-T positive patients (Sevoflurane - 9; desflurane - 6, $P \geq 0.05$) were comparable. Post-operative MPI indicated decreased left ventricular function in sevoflurane group as compared to desflurane group ($P \leq 0.03$). **Conclusion:** Desflurane exerts better cardioprotective effect than sevoflurane as indicated by better MPI in OPCAB surgeries.

Key words: Creatine phosphokinase, desflurane, myoglobin, myocardial performance index, perioperative myocardial ischemia, sevoflurane, troponin T

INTRODUCTION

Perioperative myocardial ischaemia (PMI) is a serious complication of cardiac surgery, which considerably increases the risk of mortality and morbidity.[1] Patients with a history of PMI are at a higher risk of experiencing early complications than others. The probability of remaining free of newer cardiac events in those with a history of PMI was 51% compared with 96% in patients without a PMI.[2] The length of hospital stay is also considerably prolonged in patients with perioperative cardiac complications.[3]

While several therapeutic agents are able to target certain events triggering PMI, they are unable to prevent PMI in all circumstances. This has led researchers to try alternative approaches of making the myocardium resistant to ischaemic damage, irrespective of the trigger.[3]

Myocardial protection is an area, which being widely researched currently to prevent or reduce the incidence of perioperative ischemic complications.[3] The term ischaemic pre-conditioning coined by Murry *et al.* refers to the phenomenon where brief episodes of sublethal ischaemia render the heart more resistant to subsequent prolonged ischaemic injury.[4,5]

How to cite this article: Sivanna U, Joshi S, Babu B, Jagadeesh AM. A comparative study of pharmacological myocardial protection between sevoflurane and desflurane at anaesthestic doses in patients undergoing off pump coronary artery bypass grafting surgery. Indian J Anaesth 2015;59:282-6.

Such myocardial protection can be mimicked by some of the pharmacological agents. Over the last decade, it has become clear that volatile anaesthetic agents are protective in the settings of PMI and reperfusion. The American College of Cardiology Foundation/American Heart Association 2011 guideline for coronary artery bypass surgery has recommended the use of volatile anaesthetic agents for fast tracking in uncomplicated procedures (Class IIa, level of evidence A). Furthermore, there is evidence that the choice of volatile anaesthetics in the anaesthetic regimen is associated with better outcome after cardiac surgery.[6]

The classical phenomenon of pre-conditioning documented in experimental models can be reproduced to an extent in coronary surgeries using cardiopulmonary bypass. In such situations, the pre-conditioning agent can be used for some time before the cross-clamp is applied (the ischaemic period). Removal of the cross-clamp defines the reperfusion period. The same pattern of ischaemia-reperfusion injury to the myocardium cannot be reproduced in off-pump coronary artery bypass grafting (OPCAB). In the setting of OPCAB, the periods of ischemia and reperfusion are difficult to clearly delineate because episodes of ischaemia are frequently alternated with episodes of reperfusion.[7]

A review article demonstrated that repeated exposure of the myocardium to a volatile anaesthetic agent significantly protects the myocardium against ischemia -reperfusion injury.[8]

Hence, we planned to study the effect of two different commonly used volatile anaesthetics (desflurane and sevoflurane) as myocardial protective agents in OPCAB surgery. We also assessed the myocardial protective effect in the early and the late myocardial protection window periods. The early protection was evaluated by sensitive cardiac blood markers such as troponin T (Trop-T) and creatine phosphokinase-MB (CPKMB or CPK-MB). Late window period protection was assessed by myocardial performance index (MPI) echocardiographically.

METHODS

This prospective randomised study was performed at a tertiary cardiac centre, during 2010–2011 after ethical clearance from the Institutional Ethics Committee. Written informed consent was obtained from all patients prior to the study. Patients scheduled to undergo elective OPCAB surgery were enrolled for the study. Patients with ejection fraction <40%; those undergoing repeat coronary surgery and concurrent surgeries were excluded from the study.

Based on previous studies[9-11] and considering the differences in MPI of 0.1 between the groups as significant clinically and 80% power (α error - 0.05 and β error - 0.20) for the study, we derived at sample size of 40 cases. They were randomly allocated based on computer randomization into two groups - Group A (n = 20) and Group B (n = 20). Antiplatelet therapy was stopped 1-week before the operation and replaced by a daily dose of 0.6 ml low molecular weight heparin, subcutaneously. Oral antidiabetic drugs were stopped 2 days prior and replaced with insulin therapy. None of the patients included were receiving theophylline therapy.

All pre-operative cardiac medications were continued until the morning of surgery. Pre-operative MPI values were analysed by echocardiography on the previous day of surgery. All patients received standard pre-medication of 10 mg oral diazepam, on the day of surgery, 2 h prior to induction.

In the operating room, patients underwent routine monitoring including five lead electrocardiography, invasive blood pressure monitoring and pulmonary artery pressure monitoring with continuous cardiac output measurement. Pulse oximetery, capnography, urine output, temperature monitoring, and electrodes for bispectral index (BIS) monitoring.

All patients received intravenous injections of midazolam (0.05 mg/kg), vecuronium (0.1 mg/kg), fentanyl (5 μg/kg), and incremental doses of propofol to achieve BIS of 40-60. Injection fentanyl and injection vecuronium bromide infusion of 1 μg/kg/h and 0.05 mg/kg respectively were used for maintenance. Group A received sevoflurane and Group B received desflurane at 0.3–2 minimum alveolar concentration to maintain intra-operative BIS of 40–60.

Haemodynamics were maintained with vasodilators and inotropes to achieve a mean arterial blood pressure (MAP) of 65–70 mm Hg. Continuous infusion of injection nitroglycerine (0.1 μg/kg/min) was administered. Injection noradrenaline was used as inotrope to maintain MAP 60–70 mmHg.

Baseline measurement of Trop-T and CPKMB were done pre-operatively. Second samples for

CPKMB and Trop-T were again obtained after 1 h and 8 h, respectively, after the operation for early window protection. While Trop-T was measured by chemiluminescence method, CPKMB was evaluated by the photoelectric method.

For a late window, all patients were assessed by echocardiography for the MPI [Figure 1], pre-operatively and post-operatively (on third day). The MPI is defined as the summation of isovolumetric contraction time and isovolumetric relaxation time and ejection time (ET) divided by ET, which is independent of heart rate, pre-load, and afterload.[12]

All echocardiographic assessments were done by single echocardiographer for uniformity.

Chi-square/Fisher exact test was used to find the statistical significance of study parameters.

RESULTS

Demographic data, baseline EF, CPKMB, Trop T were comparable in Groups A and B [Table 1].

Intra-operative haemodynamic parameters and BIS scores were comparable among the groups [Figure 2]. Inotrope scores were comparable intra-operatively, and on days 1 and 3.

Pre-operative CPKMB (27.1 ± 0.49 u/L vs. 24.6 ± 2.1 u/L; $P > 0.05$), Trop-T (0 ng/ml vs. 2 ng/ml; $P > 0.05$) and MPI (0.61 ± 0.11 vs. 0.66 ± 0.11, $P > 0.05$) were comparable in either groups and there was no significant difference between these values ($P = 0.166$). The mean pre- and post-CPKMB in sevoflurane group were 27.1 ± 1.82 u/L and 29.05 ± 5.2 u/L, respectively ($P = 0.135$). Post-operative Trop-T values indicating ischaemia was seen in 9 patients (sevoflurane) vs. 6 patients (desflurane) ($P > 0.05$). Post-operative CPKMB was significant in the sevoflurane group ($n = 7$ vs. $n = 5$, $P > 0.05$). Inotrope scores on day 0 ($P = 0.41$), day 1 ($P = 0.61$), and day 3 ($P = 0.69$) were comparable [Table 1].

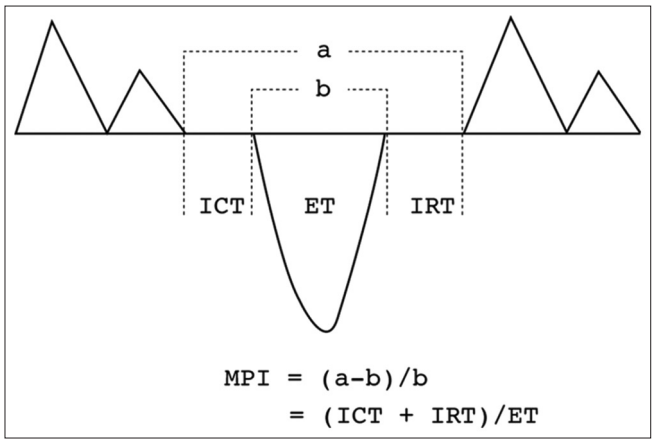

Figure 1: Calculating myocardial performance index (MPI). Cessation to onset of mitral inflow is represented by the interval 'a' and it is the sum of isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET). Interval 'b' represents the left ventricular outflow velocity tracing (ET) (From http://lan.sagepub.com/cgi/content-nw/full/43/2/127/LA06001EF6)

Myocardial performance index changes recorded as a change from the pre-operative values were compared by cross tabulations, and Pearson Chi-square test was applied to evaluate the significance. There was a statistically significant change between the two groups ($P = 0.013$).

Duration of ventilation ($P = 0.17$), length of ICU stay ($P = 1$), and length of hospital stay ($P = 0.16$) were lesser in the desflurane group but did not have statistical significance.

The post-operative MPI values when compared to pre-operative values, showed significant changes in both the groups. The MPI had increased in both the groups post-operatively. However, there was a greater increase in the sevoflurane group compared to the desflurane group.

Changes in MPI from baseline values were compared by cross tabulations and Pearson Chi-square test was applied to find a significance. A value of 0.14 difference between the baseline and post-operative period was considered a significant change. This was the difference reported between normal subjects and

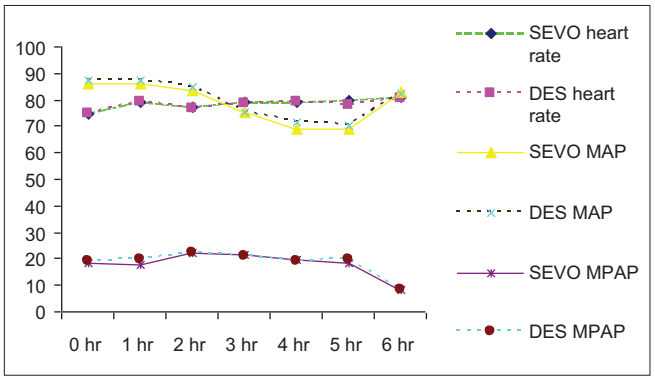

Figure 2: Line graph depicting haemodynamic parameters between groups in the intra-operative period. SEVO – Sevoflurane; DES – Desflurane; MAP – Mean arterial pressure; MPAP – Mean pulmonary artery pressure

patients with multivessel coronary artery disease. There was a statistically significant change ($P = 0.013$) between the two groups [Table 2].

DISCUSSION

The primary goal of this study was to assess the better inhalational agent between sevoflurane and desflurane for pharmacological myocardial protection. To investigate the same, we divided the post-operative period into early and late window periods. Early markers of myocardial injury were troponin and CPKMB and late period was evaluated by MPI. Desflurane and sevoflurane were comparable in myocardial protection in early period, but desflurane showed a better myocardial protective efficacy in late window period.

Myocardial protection noted following the administration of volatile anaesthetics has been attributed to the reduction in ischaemia-reperfusion injury or to the pre-conditioning effect on the myocardium.[7] Some of the mechanisms by which the volatile agents may offer myocardial protection is by opening of mitochondrial K_{ATP} channels, increasing the mitochondrial reactive oxygen species (ROS), activation or translocation of tyrosine kinases, protein kinase C, and p_{38} mitogen-activated protein kinase, mediating nitric oxide release and suppression of neutrophil activation, neutrophil–endothelium interactions.[7]

Troponin flux, which is often noted following acute myocardial infarction, has been considered as a sensitive marker of myocardial damage.[13] Elevations in troponin and CKMB levels and prolonged post-operative ischaemia during the initial post-operative days can predict the increased risk of long-term mortality following major vascular surgeries.[14]

Myocardial performance index assesses both systolic and diastolic function of the myocardium and hence is a global performance indicator.[12,15] Myocardial dysfunction increases isovolaemic times and the resultant increase in MPI index. MPI as an indicator of cardiac ischaemia and as a surrogate has shown a direct correlation with invasive measurements in human stress echocardiography studies.[16]

To our present knowledge, this is first clinical study to evaluate pharmacological protection in off-pump coronary surgery comparing two inhaled anaesthetic drugs, with CPKMB and Trop-T as markers for early window and MPI as marker for late window of myocardial protection.

A meta-analysis of myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery found sufficient evidence to suggest that volatile anaesthetic agents such as sevoflurane and desflurane do provide myocardial protection in CABG surgery with significant increase in post-bypass cardiac index and reduction in troponin levels, inotrope use and duration of ventilation.[7]

A review of cardiac protection by volatile anaesthetics concluded that all volatile anaesthetics induce dose-dependent depression in myocardial contractility and, therefore, have a beneficial role on myocardial ischaemia.[6]

A meta-analysis of myocardial protection with volatile anaesthetic agents during coronary artery bypass

Table 1: Demographic profile and clinical characteristics of the groups

Variable	Sevoflurane (Group A)	Desflurane (Group B)	*P*
Age (years)	66.25±6.64	65.8±5.26	0.81
Weight (kg)	65.75±8.62	64.65±8.5	0.67
BSA (kg/m^2)	1.50±0.22	1.47±0.20	0.25
Ejection fraction (%)	57.65	56.95	0.63
CPKMB (u/L)			
Pre	27.1±0.49	24.6±2.5	>0.05
Post	29.05±5.26	30.85±26.9	0.77
Trop T (ng/ml) positive patients			
Pre	0	2	>0.05
Post	9	6	0.32
MPI			
Pre	0.61±0.11	0.66±0.11	0.16
Post	0.66±0.168	0.64±0.19	0.81
Inotrope score			
Day 1	6.05±1	5.75±1.2	0.41
Day 2	4.25±0.9	4.1±0.9	0.61
Day 3	1.85±0.9	1.6±1.3	0.49
Ventilation (h)	514.0±95	472.0±0.92	0.17
ICU stay (days)	3.0±0.56	3.0±0.72	1.0
Hospital stay (days)	7.45±0.82	7.1±0.71	0.16

MPI – Myocardial performance index; CPKMB – Creatinine phophokinase MB type; Trop T – Troponin T; BSA – Body surface area; ICU – Intensive Care Unit

Table 2: Cross tabulation showing the change in MPI from pre-operative to post-operative 3rd day values

MPI change cross tabulation	Group		Total
	Sevoflurane (A)	Desflurane (B)	
MPI pre versus post			
Same	13	15	28
Improved	0	4	4
Deteriorated	7	1	8
Total (*P*=0.013)	20	20	40

MPI – Myocardial performance index

surgery revealed increase in post-bypass cardiac index and reduced troponin flux following the administration of volatile anaesthetics.This indicates the myocardial protection conferred by these agents.[7] A study showed ROS mediate sevoflurane- and desflurane-induced pre-conditioning in isolated human right atria *in vitro*.[17]

In the present study, both CPKMB and Trop-T values as early window markers did not show statistically significant difference between the two groups. This confirms the myocardial protection of the two inhaled agents in our cohort. However, when assessed for late post-operative period MPI, there was 'statistically' significant higher number of cases with 'no change' and 'improved MPI' in desflurane group. Change in MPI of 0.14 in comparison to post-operative MPI was considered as 'clinically' significant.[12,15,18]

As assessed by MPI on third post-operative day, global myocardial performance was preserved, improved or deteriorated in 15, 4, 1 number of patients in desflurane group as compared to 13, 0, 7 patients respectively in sevoflurane group with statistical significance *(P* = 0.013). Even though the early post-operative period showed no difference in protection by either agent, the late post-operative period assessment shows better preservation of myocardial performance in desflurane group.

Desflurane pre-conditioning of human myocardium against simulated ischaemia basically occurs through the activation of mitochondrial K_{ATP} channels and modulation of adenosine A_1 receptors.[12] Further, desflurane-induced protection also involves modulation of adrenoceptors in contrast with other volatile anaesthetics.[19] Therefore, the indices may have been better with desflurane.

CONCLUSION

Desflurane exerts a better cardioprotective effect than sevoflurane as indicated by better MPI in the late window period, whereas they have similar protective effect in early window period after OPCAB surgeries.

REFERENCES

1. Effects of acadesine on the incidence of myocardial infarction and adverse cardiac outcomes after coronary artery bypass graft surgery. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. Anesthesiology 1995;83:658-73.
2. Guiteras Val P, Pelletier LC, Hernandez MG, Jais JM, Chaitman BR, Dupras G, *et al*. Diagnostic criteria and prognosis of perioperative myocardial infarction following coronary bypass. J Thorac Cardiovasc Surg 1983;86:878-86.
3. Walsh SR, Tang T, Sadat U, Dutka DP, Gaunt ME. Cardioprotection by remote ischaemic preconditioning. Br J Anaesth 2007;99:611-6.
4. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: A delay of lethal cell injury in ischemic myocardium. Circulation 1986;74:1124-36.
5. Huffmyer J, Raphael J. Physiology and pharmacology of myocardial preconditioning and postconditioning. Semin Cardiothorac Vasc Anesth 2009;13:5-18.
6. Landoni G, Fochi O, Torri G. Cardiac protection by volatile anaesthetics: A review. Curr Vasc Pharmacol 2008;6:108-11.
7. Symons JA, Myles PS. Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: A meta-analysis. Br J Anaesth 2006;97:127-36.
8. De Hert SG. Volatile anesthetics and cardiac function. Semin Cardiothorac Vasc Anesth 2006;10:33-42.
9. Conzen PF, Fischer S, Detter C, Peter K. Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. Anesthesiology 2003;99:826-33.
10. De Hert SG, ten Broecke PW, Mertens E, Van Sommeren EW, De Blier IG, Stockman BA, *et al*. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. Anesthesiology 2002;97:42-9.
11. Tomai F, De Paulis R, Penta de Peppo A, Colagrande L, Caprara E, Polisca P, *et al*. Beneficial impact of isoflurane during coronary bypass surgery on troponin I release. G Ital Cardiol 1999;29:1007-14.
12. Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: Correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr 1997;10:169-78.
13. Etievent JP, Chocron S, Toubin G, Taberlet C, Alwan K, Clement F, *et al*. Use of cardiac troponin I as a marker of perioperative myocardial ischemia. Ann Thorac Surg 1995;59:1192-4.
14. Landesberg G, Shatz V, Akopnik I, Wolf YG, Mayer M, Berlatzky Y, *et al*. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42:1547-54.
15. Tei C, Ling LH, Hodge DO, Bailey KR, Oh JK, Rodeheffer RJ, *et al*. New index of combined systolic and diastolic myocardial performance: A simple and reproducible measure of cardiac function – A study in normals and dilated cardiomyopathy. J Cardiol 1995;26:357-66.
16. Broberg CS, Pantely GA, Barber BJ, Mack GK, Lee K, Thigpen T, *et al*. Validation of the myocardial performance index by echocardiography in mice: A noninvasive measure of left ventricular function. J Am Soc Echocardiogr 2003;16:814-23.
17. Hanouz JL, Zhu L, Lemoine S, Durand C, Lepage O, Massetti M, *et al*. Reactive oxygen species mediate sevoflurane-and desflurane-induced preconditioning in isolated human right atria *in vitro*. Anesth Analg 2007;105:1534-9.
18. Dagdelen S, Eren N, Karabulut H, Caglar N. Importance of the index of myocardial performance in evaluation of left ventricular function. Echocardiography 2002;19:273-8.
19. Hanouz JL, Yvon A, Massetti M, Lepage O, Babatasi G, Khayat A, *et al*. Mechanisms of desflurane-induced preconditioning in isolated human right atria *in vitro*. Anesthesiology 2002;97:33-41.

Source of Support: Nil, **Conflict of Interest:** None declared