Original Article

A Randomized Controlled Trial Comparing the Myocardial Protective Effects of Isoflurane with Propofol in Patients Undergoing Elective Coronary Artery Bypass Surgery on Cardiopulmonary Bypass, Assessed by Changes in N-Terminal Brain Natriuretic Peptide

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Abstract

Objective: The objective of the study is to compare the myocardial protective effects of isoflurane with propofol in patients undergoing elective coronary artery bypass surgery on cardiopulmonary bypass (CPB), the cardio protection been assessed by changes in N-terminal brain natriuretic peptide (NT proBNP). **Methodology and Design:** This study is designed as a participant blinded, prospective randomized clinical trial. **Setting:** Christian Medical College Hospital, Vellore, India. **Participants:** Patients undergoing elective coronary artery bypass surgery on CPB. **Intervention:** Anesthesia was maintained with 0.8–1.2 end tidal concentrations of isoflurane in the isoflurane group and in the propofol group, anesthesia was maintained with propofol infusion as described by Roberts *et al*. **Measurements:** Hemodynamic data were recorded at frequent intervals during the surgery and up to 24 h in the Intensive Care Unit (ICU). The other variables that were measured include duration of mechanical ventilation, dose and duration of inotropes in ICU, (inotrope score), duration of ICU stay, NT proBNP levels before induction and 24 h postoperatively, creatine kinase-MB levels in the immediate postoperative, first and second day. **Results:** Mean heart rate was significantly higher in propofol group during sternotomy, (P = 0.021). Propofol group had a significantly more number of patients requiring nitroglycerine in the prebypass period (P = 0.01). The increase in NT proBNP from preoperative to postoperative value was lesser in the isoflurane group compared to propofol even though the difference was not statistically significant. The requirement of phenylephrine to maintain mean arterial pressure within 20% of baseline, mechanical ventilation duration, inotrope use, duration of ICU stay and hospital stay were found to be similar in both groups. **Conclusion:** Propofol exhibit comparable myocardial protective effect like that of isoflurane in patients undergoing coronary artery bypass graft surgery. Considering the unproven mortality benefit of isoflurane and the improved awareness of green OT concept, propofol may be the ideal alternative to volatile anesthetics, at least in patients with good left ventricular function.

Keywords: *Coronary artery bypass grafting, isoflurane, myocardial protection, N-terminal brain natriuretic peptide, propofol*

Introduction

Perioperative myocardial ischemia during elective coronary artery bypass graft (CABG) can occur in the prebypass period, during bypass and in the postbypass period. Reperfusion of the myocardium after an ischemia induces myocardial apoptosis and resultant increase in infarct size through the reperfusion injury, despite the restoration of coronary blood flow.[1,2]

To minimize the myocardial ischemia during CABG, multiple strategies are often employed by the perioperative team. Volatile anesthetics have been shown to confer myocardial protection against reperfusion injury through anesthetic-induced pre- and post-conditioning mechanism.[3,4] Animal studies have shown that propofol offers myocardial protection from ischemia-reperfusion injuries.[5]

We wanted to evaluate the myocardial protective effects of isoflurane versus propofol in patients undergoing elective coronary artery bypass surgery on cardiopulmonary bypass (CPB). Cardio protection was assessed by changes in N-terminal brain natriuretic peptide and creatinine kinase-MB (CK-MB).[6,7]

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Aim and objectives

The primary aim of this study was to compare the two anesthetic regimens, consisting of propofol and Isoflurane on the degree of myocardial preservation, which were analyzed by changes in the perioperative levels of N-terminal brain natriuretic peptide (NT proBNP) and CK-MB.

Secondary objectives include hemodynamic stability, inotropic support requirement and duration of endotracheal intubation beyond overnight ventilation as well as Intensive Care Unit (ICU) stay.

Methodology

This was a prospective randomized study which was approved by the institutional ethics committee. 52 patients were recruited into the study after a written informed consent. This study deals with two different anesthetic regimens, Isoflurane (Group I) versus propofol (Group P) in a patient undergoing CABG with CPB. Based on the study by De Hert *et al*.,[8] a sample size of 26 was required in each group. Consenting adults between 18 and 70 years scheduled to undergo elective CABG were recruited into the study. While patients with reduced left ventricular (LV) function (ejection fraction <40%), patients with recent myocardial infarction (<6 weeks), hemodynamic instability requiring medical or mechanical supports, acute congestive cardiac failure, chronic kidney disease as indicated by serum creatinine >1.5 mg% and chronic obstructive pulmonary disease as shown by FEV1 <50% were excluded from the study.

Anesthesia protocol

All preoperative cardiac medication except ACE inhibitors was continued till the morning of surgery. Patients were premedicated with lorazepam 2 mg and omeprazole 20 mg on the night before the surgery along with lorazepam 2 mg 60 min before induction. For patients above 60 years, lorazepam 1 mg was given at night instead of 2 mg. Anesthesia technique was standardized with midazolam (0.15–0.3 mg/kg) and fentanyl (5–10 μg/kg) for induction and endotracheal intubation.

Monitoring used during the CABG procedure include pulse oximetry, ECG, arterial blood pressure (both radial and femoral), Bi-spectral index monitoring, capnography, central venous pressure (CVP) monitoring, temperature, and urine output.

After endotracheal intubation, anesthesia was maintained according to the protocols in two groups. In isoflurane group, anesthesia was maintained with 0.8-1.2 end tidal concentrations of isoflurane and in propofol group, anesthesia was maintained with propofol infusion as described by Roberts *et al*., which is 10 mg/kg/h for the first 10 min followed by 8 mg/kg/h for the next 10 min and thereafter at 6 mg/kg/h.[9] Both groups received fentanyl infusion at 1 μg/kg/h and incremental dose of fentanyl were given to blunt the surgical stress response. Anesthesia was titrated to maintain a BIS value about 40–60 throughout the CABG procedure. The administration of vasoactive drugs (phenylephrine/ephedrine) or Glyceryl trinitrate (GTN) for maintenance of hemodynamics during the prebypass period were done in both groups whenever required.

CABG was performed under CPB with the pump flow of 2–2.4 L/m^2/min under mild hypothermia of 32°C–34°C in both groups with the Activated Clotting Time (ACT) maintained >480 s throughout the bypass period. Anesthesia was maintained with either propofol infusion or with isoflurane through the CPB oxygenator during bypass with BIS target of 40–60. St. Thomas root cardioplegia was used for inducing cardiac arrest in both the groups and it was repeated every 20 min. Perfusion pressure during CPB was maintained between 50 and 70 mmHg with intermittent phenylephrine or by noradrenaline infusion. Hematocrit was maintained >21% during CPB with or without adding packed cells and the acid base management during CPB was done by alpha stat method.

Adrenaline infusion was started at the beginning of the last proximal anastomosis, by that time the heart has already started beating after the release of cross clamp. In all the patients, adrenaline was started at a dose of 0.1 mcg/kg/min as per our institutional protocol and surgeon's preference. The adrenaline infusion was then titrated down according to hemodynamics. After making sure that the patients were adequately rewarmed (nasopharyngeal temperature of 36.0°C) along with normal acid blood gas measurement, Patients were weaned off from the bypass and the residual heparin was then reversed with protamine at the dose of 1:1 ratio and if needed, additional dose of protamine were given if the postprotamine ACT was more than baseline ACT. Post-CABG procedure the patients were shifted to ICU where the patients were weaned from inotropic support and ventilator support as per the institutional protocol.

Data collection

Baseline heart rate and mean arterial pressure (MAP) were recorded before induction with CVP postintubation after securing the central venous access. Hemodynamic data are then recorded at frequent intervals during the intraoperative period starting from induction, intubation, skin incision, sternotomy, and chest closure. In the ICU, vital signs were monitored at 1 h, 6 h, 12 h, and last at 24 h. The other variables that were measured include duration of mechanical ventilation, dose and duration of inotropes in ICU, (inotrope score), duration of ICU stay, NT proBNP levels before induction and 24 h postoperatively, creatine kinase-MB (CK-MB) levels in the immediate postoperative, first and second day.

Statistical analysis

Descriptive statistics were obtained for all study variables. All patient characteristics and other variables such as hemodynamic data, inotropic support, level of biochemical marker, and postoperative ICU stay were compared between the study groups using Mann–Whitney test. $P < 0.05$ was considered statistically significant. All analyses was done using SPSS version 16.0 (IBM Corporation, USA) for Microsoft windows.

Results

The two groups in this study were designated as group P and group I for propofol and isoflurane respectively. The total size of the study population is 46 with 23 in each group. The patients recruited in both groups included single, double as well as triple vessel disease (1:2:20 in Group P vs. 0:3:20 in Group I). The demographic data, comorbid conditions, New York Heart Association functional status, CPB time, aortic cross clamp time were comparable between the two groups [Table 1].

The mean heart rate recorded at various points in the perioperative period from skin incision up to 24 h into ICU was almost similar in both groups. However, the mean heart rate was significantly higher in propofol group during sternotomy, ($P = 0.021$) [Tables 2a and b].

Fifteen patients in propofol group and 17 patients in isoflurane group received phenylephrine during prebypass period and the requirement of phenylephrine to maintain MAP within 20% of baseline was not statistically different between the groups ($P = 0.079$) by Mann–Whitney test [Tables 3 and 4].

Group P had a significantly more number of patients requiring GTN in the prebypass period ($P = 0.01$) (20 patients in Group P and 14 patients in Group I in the prebypass period, respectively) [Tables 5-7].

Vasopressor requirement (Phenylephrine and noradrenaline) requirement during the CPB was similar between the groups. Inotropic requirement during the postbypass period (inotrope score) was similar in both groups and it was not found to be statistically significant by Mann–Whitney test.

The mean value of preoperative NT proBNP was 258.81 ± 246.15in propofol group and 355.38 ± 362.58 in isoflurane group, respectively ($P = 0.235$). The mean value of postoperative NT proBNP was 2108.43 ± 1560.82 in propofol group and 2276.5 ± 2219.38 in isoflurane group ($P = 0.709$). The mean of difference between the postoperative increases from preoperative level was 1849.62 ± 1453.37 in propofol group P and 1920.97 ± 2150.278 in isoflurane group ($P = 0.287$). The mean of % increase of NT proBNP from preoperative baseline value to postoperative value was 88.2% in propofol group P and 64.1% in isoflurane group I ($P = 0.318$).

Table 1: Demographic data

Variables	Group P	Group I
Age (year)	53.7±7.11	57.8±6.9
Sex ratio (male:female)	19:4	19:4
Weight	67.3±10.9	61.6±8.7
NYHA Class (2:3)	9:14	12:11
Number of vessels involved (1:2:3)	1:2:20	0:3:20
Left main disease (*n*)	9	7
Ejection fraction (%)	54.8±3.9	58.3±6.03
Previous PTCA (*n*)	3	5
Diabetes (*n*)	12	11
COPD (*n*)	2	1
Medications (*n*)		
Beta - blockers	23	22
ACE - I	18	19
Calcium channel blockers	5	2
Nitrates	18	21
Diuretics	2	2
Statins	18	17
OHA/insulin	14	13
Bronchodilators	2	1
Duration of aortic × clamp	41.30±9.94	47.17±9.19
Duration of CPB	79.13±16.82	89.78±18.56
Number of CPB's (1:2)	22:1	22:1
Number of grafts (1:2:3:4)	1:1:16:5	0:1:19:3

NYHA: New York Heart Association, PTCA: Percutaneous Transluminal Coronary Angioplasty , ACE: Angiotensin-converting-enzyme, OHA: Oral hypoglycemic agent, CPB: Cardiopulmonary bypass, COPD: Chronic obstructive pulmonary disease

Table 2a: Heart rate

Various events	Group P	Group I
Baseline	74.21±12.48	69.86±11.24
Induction	70.04±12.78	65.1±10.82
Intubation	72.21±16.01	65.56±16.86
Skin incision	70.1±10.77	64.47±10.32
Sternotomy	75.17±13.56	66.21±11.66
Chest closure	104.91±13.28	101.7±13.6
Time after admission into the ICU		
T1 (1 h)	107.8±13.31	104.9±17.48
T6 (6 h)	103.21±16.46	98.3±17.73
T12 (12 h)	98.73±16.55	97±14.3
T24 (24 h)	94.56±22.96	97.82±12.85

ICU: Intensive Care Unit

These differences were not found to be statistically significant [Tables 8-10].

The increase in NT proBNP from preoperative to postoperative value was less in the isoflurane group compared to propofol even though the difference is not statistically significant (6-fold increase in isoflurane group compared to 8-fold increase in propofol group).

The mean values of CK-MB levels in the immediate postoperative period was 63.43 ± 15.86 versus

Tables 2b: Mean arterial pressure

Various events	Group P	Group I
Baseline	96.1±13.9	94.39±13.76
Induction	89.1±16.9	82.13±17.36
Intubation	84±12.38	80.56±11.70
Skin incision	82.04±11.84	77.21±10.32
Sternotomy	83.43±8.75	82.17±9.70
Chest closure	77.47±7.86	72.4±10.1
Time after admission into ICU		
T1 (1 h)	92.43±13.06	88.6±8.88
T6 (6 h)	82.65±10.83	84.39±8.22
T12 (12 h)	84.9±8.33	80.52±8.91
T24 (24 h)	87.26±11.67	83±11.20

ICU: Intensive Care Unit

Table 3: Phenylephrine requirements

Group	PNP (average number of bolus administration)		
	Pre-CPB	CPB	Post-CPB
P	2.17±2.40	5.56±4.78	1.73±2.17
I	4.73±4.78	8.43±7.29	8.43±7.29

PNP: Phenylephrine, CPB: Cardiopulmonary bypass

Table 4: Mann–Whitney test statistics for phenylephrine

	PNP		
	Pre	CPB	Post
Mann–Whitney U-test	186.000	231.500	263.000
Wilcoxon W	462.000	507.500	539.000
Z	−1.756	−0.731	−0.035
Asymptotic significant (two-tailed)	0.079	0.464	0.972

PNP: Phenylephrine, CPB: Cardiopulmonary bypass

70.43 ± 20.13 (P = 0.184), while on first postoperative day, it was 41.34 ± 25.14 versus 43.69 ± 29.60 (P = 0.709) and on second postoperative day, it was, 34.91 ± 13.69 versus 40 ± 22.03 (P = 0.517) in propofol group, and isoflurane group, respectively. Statistical analysis using Mann–Whitney test, Kolmogrov–Smirnov and Wald–Wolfowitz test showed that changes in CK-MB levels were not statistically significant between both groups [Tables 11-13].

Mechanical ventilation duration, inotrope use, duration of ICU stay and hospital stay were found to be similar in both groups.

Discussion

We did a prospective randomized control study to compare the myocardial protective effects of two anesthetic agents (propofol vs. isoflurane) in patients undergoing myocardial revascularization under CPB using NT proBNP and CK-MB as the markers. BIS monitoring was used apart from other ASA standard monitoring as the incidence of awareness under anesthesia in cardiac surgeries is almost 5–15 fold higher when compared to noncardiac surgery.[10] In view of differences in the "on pump" metabolism of propofol and isoflurane and unpredictable

Table 5: Nitroglycerin requirement

Group	GTN (average number of alterations)		
	Pre-CPB	CPB	Post-CPB
P	4.00±2.96	0.39±0.78	0.86±1.60
I	1.60±2.53	0.21±0.51	0.34±0.64

GTN: Glyceryl trinitrate , CPB: Cardiopulmonary bypass

Table 6: Mann–Whitney test statistics for GTN

	GTN		
	Pre	CPB	Post
Mann–Whitney U-test	101.000	240.000	239.000
Wilcoxon W	377.000	516.000	515.000
Z	−3.649	−0.748	−0.707
Asymptotic significant (two-tailed)	0.000	0.454	0.480

GTN: Glyceryl trinitrate, CPB: Cardiopulmonary bypass

Table 7: Two-sample Kolmogorov–Smirnov test for GTN

	GTN		
	Pre	CPB	Post
Most extreme differences			
Absolute	0.565	0.087	0.174
Positive	0.000	0.000	0.000
Negative	−0.565	−0.087	−0.174
Kolmogorov–Smirnov *Z*	1.917	0.295	0.590
Asymptotic significant (two-tailed)	0.001	1.000	0.878

GTN: Glyceryl trinitrate, CPB: Cardiopulmonary bypass

extrahepatic metabolism of propofol, BIS value was used as a better quantifiable measure of effect site concentration for assessment of depth of anesthesia. Propofol or volatile anesthetics were administered continuously throughout the CABG as it was shown to exhibit better myocardial protective effect rather than the intermittent administration.[11]

The patient's demographic data, comorbid condition, number of diseased coronaries, ejection fraction, CPB time, aortic cross clamp time, and number of coronaries grafted were similar in both groups.

The hemodynamic parameters recorded at various points in the perioperative period from skin incision up to 24 h into ICU were almost similar in both groups. It is purely coincidental that the hemodynamic data in both groups seemed to be identical, which could be due to the better preoperative optimization achieved with beta blockers in the patients in both the groups. On comparison of hemodynamic data during the perioperative period, the mean heart rate during sternotomy was significantly higher in propofol group and the MAP during the aortic cannulation time was higher in propofol group P requiring frequent intervention with (nitro-glycerine) GTN. A significantly more number of patients in propofol group received GTN compared to isoflurane group during the prebypass period. The hemodynamic changes that occur during the prebypass period with the two anesthetic agents may be explained by

Table 8: Descriptive statistics (N-terminal prohormone of brain natriuretic peptide)

Group	*n*	Minimum	Maximum	Mean	Median	SD
P						
BNP preoperative	23	20.7	823.0	258.812	192.000	246.1525
BNP postoperative	23	568	6881	2108.43	1442.000	1560.821
BNP difference	23	376.0	6531.0	1849.623	1291.600	1453.3730
BNP percentage increase	23	195.833	6876.294	1583.71143	1040.23700	1694.498508
Valid N (list wise)	23					
I						
BNP preoperative	23	44.2	1506.0	355.377	239.000	362.5811
BNP postoperative	23	546	10696	2276.35	1464.00	2219.386
BNP difference	23	461.0	10186.6	1920.970	1027.900	2150.2781
BNP percentage increase	23	63.586	9564.931	1422.56383	631.02900	2202.159722
Valid N (list wise)	23					

BNP: Brain natriuretic peptide, SD: Standard deviation

Table 9: Mann–Whitney test statistics (N-terminal prohormone of brain natriuretic peptide)

	BNP preperative	BNP postperative	BNP difference	BNP percentage increase
Mann–Whitney U-test	210.500	247.500	216.000	219.000
Wilcoxon W	486.500	523.500	492.000	495.000
Z	−1.186	−0.373	−1.066	−1.000
Asymptotic significant (two-tailed)	0.235	0.709	0.287	0.318

BNP: Brain natriuretic peptide

Table 10: Two-sample Kolmogorov–Smirnov test statistics (N-terminal prohormone of brain natriuretic peptide)

	BNP preperative	BNP postperative	BNP difference	BNP percentage increase
Most extreme differences				
Absolute	0.217	0.174	0.304	0.174
Positive	0.217	0.087	0.087	0.043
Negative	0.000	−0.174	−0.304	−0.174
Kolmogorov–Smirnov *Z*	0.737	0.590	1.032	0.590
Asymptotic significant (two-tailed)	0.649	0.878	0.237	0.878

BNP: Brain natriuretic peptide

Table 11: Creatine kinase-MB levels

Group	CK-MB levels		
	Immediate postoperative period(1)	First Postoperative Day(2)	Second Postoperative Day(3)
P	70.43±20.13	43.69±29.60	40±22.03
I	63.43±15.86	41.34±25.14	34.91±13.69

CK-MB: Creatine kinase-MB

Table 12: Mann–Whitney test statistics creatine kinase-MB

	CK-1	CK-2	CK-3
Mann–Whitney U-test	204.000	247.500	235.000
Wilcoxon W	480.000	523.500	511.000
Z	−1.330	−0.374	−0.649
Asymptotic significant (two-tailed)	0.184	0.709	0.517

CK: Creatine kinase

relatively better antinociceptive effect of isoflurane over propofol.[12,13] The increased response seen with propofol might not be due to awareness since all the patients were premedicated adequately with lorazepam and induced with midazolam. We did not use a bolus of propofol before the initiation of propofol infusion. The 3 compartment model requires a bolus before the infusion. We may not have reached the target effect site concentration with propofol without the bolus dose at sternotomy. The maintenance of anesthesia with propofol infusion according to 10-8-6 protocol of Roberts *et al*. was found satisfactory.[9] We did not find any difficulty in maintaining the BIS between 40–60 with this regimen in any of our patients.

The base line values and the postoperative values of NT proBNP in both group were found to be almost similar. Postoperative increase of NT proBNP in propofol group was 8 fold while the raise was 6 fold in the isoflurane group, but the difference was not statistically significant. Similar results were observed in CK-MB level measured in the postoperative period between the two groups. There was no statistically significant difference in inotrope score; mechanically ventilated days and ICU stay between the groups.

Table 13: Two-sample Kolmogorov–Smirnov test statistics creatine kinase-MB

	CK-1	CK-2	CK-3
Most extreme differences			
Absolute	0.304	0.174	0.130
Positive	0.087	0.087	0.130
Negative	−0.304	−0.174	−0.130
Kolmogorov–Smirnov *Z*	1.032	0.590	0.442
Asymptotic significant (two-tailed)	0.237	0.878	0.990

CK: Creatine kinase

Our study findings suggest that the myocardial protective effects of propofol and isoflurane were comparable as the cardiac biomarker changes in the perioperative period were statistically insignificant. The perioperative changes in cardiac markers in our study corroborates with the study done by Flier *et al*. and Xia *et al*. where cardiac troponin I was used as cardiac marker.[14,15]

The mechanism of myocardial protective effect of propofol is different from volatile anesthetics and it may be attributed to its antioxidant effect, Na-H channel blockade, sarcolemmal Ca channel blockade, inhibitory effect of propofol on MPTP opening and ability to increase the protein kinase C activity in cardiomyocytes.[2,16] Our study did not show a significant myocardial protective effect of isoflurane over propofol unlike the study by De Hert *et al*., which may be attributed to variable preconditioning potencies of volatile anesthetic that increases from isoflurane over sevoflurane to desflurane as shown by Redel *et al*.

Lange *et al*. in his study on desflurane postconditioning effect showed that beta blockers, which have a class 1 recommendation for perioperative myocardial ischemia prevention, may reduce the volatile anesthetic induced postconditioning aspect of myocardial protection.[17,18] The degree of reduction of myocardial protection by the volatile anesthetics in the presence of beta blockers, whether it is the same or different to different volatile anesthetics is also exactly not known.

This study shows that propofol exhibit comparable myocardial protective effect as that of isoflurane in CABG because surgical techniques of myocardial protection between the two groups were identical. This might be due to relatively decreased preconditioning effect of isoflurane over newer volatile anesthetics. The variable pre- and post-conditioning effect of isoflurane in the presence of beta blockers may also contribute.

As reviewed by Nigro Neto *et al*., there is increased chance of operating room pollution during CPB without the proper scavenging system.[19] This would have happened in our study also with volatile anesthesia maintenance because scavenging system was not part of our CPB machine.

Limitations

Failure to derive any meaningful conclusion on duration of mechanical ventilation due to our Institutional policy to extubate the patients the next day morning.

We did not measure the cardiac index which could have reinforced the cardiac markers changes that occurred with two different anesthetic regimens since it is not a part of our institutional practice to use cardiac output monitor or transesophageal echocardiography in patients with adequate LV function.

Our data showed a wide range of nTProBN*P* values in each group. Even though all the patients recruited in our study had adequate LV systolic function, the differing levels could reflect varying degrees of diastolic dysfunction without features of failure in our patient population.

In spite of BIS not being totally validated during hypothermia, it is presumed that the decrease in BIS values would occur concurrently in both groups since there is a decrease in anesthetic requirement during hypothermia.

Conclusion

Propofol exhibit myocardial protective effects comparable to that of isoflurane in patients undergoing CABG. The relatively better myocardial protective effect of isoflurane was not getting replicated neither in morbidity nor in mortality benefit unlike newer agents such as sevoflurane and desflurane.[11] Given this unproven mortality benefit and improved awareness of green OT concept,[20,21] propofol may be the ideal alternative to volatile anesthetics, at least in patients with good LV function.

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Conflicts of interest

There are no conflicts of interest.

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