



Original Research Article

Comparison of volatile agent isoflurane vs conventional methods with intermittent propofol and benzodiazepine for BIS targeted anaesthesia on cardiopulmonary bypass

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ABSTRACT

Incidence of awareness in patients undergoing cardiac surgery is up to 23% compared to its incidence of 1% during general surgery. In our institute we conducted study in 40 patients undergoing valve surgeries and compared volatile agent vs. conventional method with help of BIS monitoring. Partly because of the difficulty of administering volatile agents during cardiopulmonary bypass (CPB), total intravenous anaesthesia (TIVA) has been a popular technique used by cardiac anaesthetists in the last few decades. However, the possibility that volatile agents cut back mortality and the incidence of myocardial infarction by preconditioning the myocardium has stimulated a revival of interest in their use for cardiac anaesthesia. We observed the higher BIS values were seen in conventional group with requirement of higher dose of propofol as a rescue to avoid intraoperative awareness. The haemodynamics were steadily maintained in isoflurane group. The inotrope score was less in isoflurane group indicating myocardial protective effect of isoflurane.

In conclusion, in patients undergoing heart surgery with CPB, the findings of this study indicate that appropriate use of isoflurane to maintained depth of anaesthesia during CPB should be monitored with use of BIS and ETAC.

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1. Introduction

Anaesthesia on cardiopulmonary bypass is a challenge. Conventionally anaesthetists use sedation like midazolam and muscle relaxant on cardiopulmonary bypass. Incidence of awareness in patients undergoing cardiac surgery is significantly higher than the overall incidence of 1% during general surgery.¹ Incidence of awareness in patients undergoing cardiac surgery is significantly higher, with older reports of up to 23%.² The incidence of intraoperative awareness during general surgery, as reported in the literature, varies between 0.1% and 0.9%.³ In our institute

we conducted study in 40 patients undergoing valve surgeries and compared volatile agent vs. conventional method with help of BIS monitoring. We also compared various other parameters like requirement of muscle relaxants, inotropes and blood lactate levels. Partly because of the difficulty of administering volatile agents during cardiopulmonary bypass (CPB), total intravenous anaesthesia (TIVA) has been a popular technique used by cardiac anaesthetists in the last few decades. However, the possibility that volatile agents cut back mortality and the incidence of myocardial infarction by preconditioning the myocardium has stimulated a revival of interest in their use for cardiac anaesthesia. Therefore, the aim of this study is to provide methods to administer volatile anaesthetic agents

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during CPB for the maintenance of anaesthesia and some of the practical issues that are involved in doing so. During study we also compared the volatile anesthetic agent with conventional method.

1.1. Review of anaesthesia on CPB

The technique of CPB was researched and developed in animals by Gibbon in the 1930s and introduced into clinical practice for heart surgery in 1953.⁴ In his early experimental work with cats, Gibbon had described his CPB equipment and had noted difficulties in maintaining anaesthesia during CPB.⁵ To overcome this problem, he passed ether vapor through the oxygenator, so establishing, in 1937, the use of a volatile anaesthetic technique during CPB. An alternative to ether was cyclopropane which had been discovered in 1929 and was also popular in thoracic anaesthesia when CPB was introduced. Despite being explosive, cyclopropane was also used to maintain anaesthesia in the early years of CPB.⁵ Initial problems experienced with CPB in humans included haemolysis associated with the original disc/bubble oxygenators and explosions due to contact between the ether or cyclopropane and the motors. For this reason, volatile anaesthesia was frequently lightened or even stopped when the patient was put on CPB. This practice gradually fell out with the introduction of halothane in 1956, which was nonexplosive and, therefore, safe to use during CPB. However, halothane brought other problems like myocardial depression, arrhythmogenicity, myocardial resistance to defibrillation and fulminant hepatitis.⁵ Since then, every new volatile agent that had been introduced into general anaesthetic practice had been applied to CPB. Isoflurane has been particularly popular, but, it has some issues like it has been concerns about its coronary steal and myocardial ischaemia.⁶ Coronary steal was one of the main motivators for the widespread adoption of total intravenous anaesthesia (TIVA) for cardiac anaesthesia in the 1990s along with the ease of administration. Like new volatile agents previously introduced into cardiac anaesthesia, TIVA was grasped with little investigation into its effect on outcome from cardiac surgery. TIVA has remained popular over the last 20 years but, recently, there has been a revival of interest in the use of volatile agents during CPB. This is because latest evidence indicates that volatile anaesthetic agents precondition the myocardium, thus reducing the incidence of myocardial infarction and mortality associated with heart surgery.⁷

1.2. Administration of volatile anaesthetics during cardiopulmonary bypass

During conduct of CPB, the circulating blood bypasses the lungs and their function is mechanically replaced by an oxygenator. Volatile anaesthetics can be administered by placing an anaesthetic vaporizer into gas supply to the

oxygenator. The end tidal anaesthetic concentration (ETAC) can be measured in exhaust port of oxygenator as shown (Figure 1).

2. Material and Methods

The study was designed at our hospital and carried out after ethical committee approval. Informed consent was taken before enrolling patients in the study.

We performed a randomized, controlled study amongst patients undergoing cardiac surgery using cardiopulmonary bypass (CPB) in period of one year from 2017 and 2018. Randomization was done by flipping coin. 20 subjects were assigned to the volatile anesthetic agent group 1 who received isoflurane for anaesthesia maintenance (Isoflurane variable percentage to maintain MAC of 0.7 to 0.9 to maintain BIS between 40 to 60), while 20 subjects assigned to the control group 2 received conventional anaesthesia (Midazolam 0.2 mg/kg bolus on cardiopulmonary bypass and muscle relaxant 0.04 mg/kg vecuronium). Anaesthesia was induced intravenously in all patients with fentanyl 5 µg/kg, propofol 1 to 2 mg/kg and vecuronium 0.1 mg/kg. Isoflurane with air and oxygen at 1 L/min was used for the maintenance of anaesthesia prior to CPB. The fentanyl was used in both groups as intermittent bolus doses to maximum of 20 mcg/kg. The patient was heparinized with 300 to 400 IU heparin before going on CPB. The dose of isoflurane was varied in response to clinical signs observed in the patients and MAC around 0.7 to 0.9, but the vaporizer was never set at less than this level and the end-tidal concentration was never less than 0.7%. No further doses of vecuronium were administered unless required (checked with use of nerve stimulator intermittently with train of four ratio monitoring). Routine monitoring devices included a 5-lead electrocardiogram, pulse oximetry and a nasopharyngeal temperature probe. A catheter was inserted into a radial artery under local anaesthesia for the measurement of systemic arterial pressure and blood sampling. The BIS electrodes (BIS Covidien, USA) were applied to the forehead, according to the marker lines. The anaesthetic monitor (Phillips IntelliVue MX550) processed and displayed the BIS scores. BIS monitoring was used continuously throughout the whole cardiac surgery, but it was recorded at particular interval as per study design. Central venous lines and a urinary catheter were also inserted. The CPB circuit comprised a roller pump (Sorin), a hollow microporous polypropylene membrane oxygenator (Affinity Medtronic) and Propofol was used as intermittent rescue bolus to maintain BIS values below 60 on CPB to avoid awareness in both groups and values were used for analysis. ETCO₂ and ETAC were monitored in expiratory port of oxygenator. Requirement of total narcotic dose, amount of muscle relaxant and vasoconstrictors were noted in both groups. The requirement of inotropes and vasopressors were calculated with inotrope score and

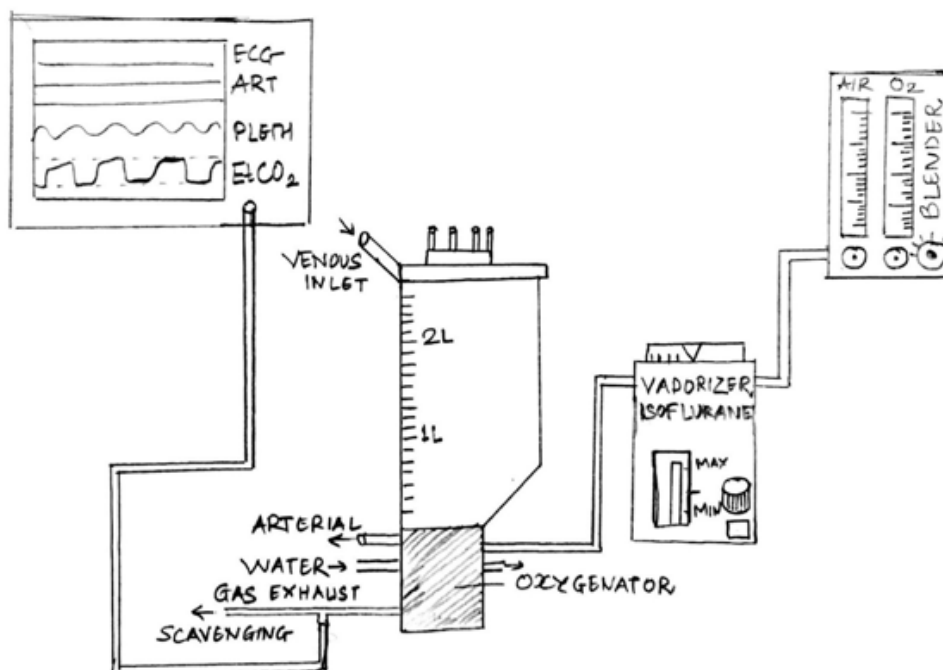


Fig. 1:

vasoactive inotropic score. Vital parameters were also compared in both groups at fixed interval. The aim was to keep full flows on cardiopulmonary bypass. The mean arterial pressures were kept around 65 mmHg with help of vasoconstrictor phenylephrine with bolus dose of 100 mcg intermittently. The patient came off from pump with adrenaline 0.02 to 0.1 mcg/kg/min to maintain mean arterial pressure around 65 mm Hg. If difficulty was there to maintain mean pressure other inotrope was added. As per choice of anaesthesiologists dopamine in the dose of 3 to 7 mcg/kg/min or noradrenaline 0.02 to 0.1 mcg/kg/min if patients are unable to maintain desired mean pressure. The vasoactive inotrope score was calculated one hour after patient had reached to cardiac recovery room. The awareness was assessed by Brice questionnaire.⁸

Inotrope Score (IS) = Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 100 x Epinephrine dose (mcg/kg/min)

Vasoactive-Inotropic Score (VIS) = IS + 10 x Milrinone dose (mcg/kg/min) + 10,000 x Vasopressin dose (units/kg/min) + 100 x Norepinephrine dose (mcg/kg/min)

2.1. Data collection and integrity

Basic demographic and clinical data were collected. The data was collected in Microsoft excel. The analysis was done with SSPS software. Statistical analysis was performed using an unpaired t-test and χ^2 where appropriate.

3. Results

All 40 patients completed the study. All patients were demographically comparable (Table 1).

Higher mean blood pressures were seen in conventional method. It was clinically significant on pump. Preoperative and post operative mean blood pressures were comparable. BIS values on pump were maintained around 40 to 60 in isoflurane group. The higher BIS values were seen in conventional method. This was statistically significant. Preoperative and postoperative values were statistically comparable. End tidal CO₂ were statistically comparable. The MAC value was maintained 0.7 to 0.8 in isoflurane group. The end tidal isoflurane concentration E_i was around 0.9 to 1. Higher lactate was seen in conventional method and was not statistically significant. Significantly higher amount of propofol, midazolam and muscle relaxant were used in conventional method. A higher dose of phenylephrine was used in isoflurane group. The inotrope score was seen higher in conventional method but was not statistically significant.

4. Discussion

In the current study, isoflurane was compared with conventional method. None of the patients in either group experienced awareness. Assuring amnesia and avoiding awareness requires an accurate assessment of anaesthetic depth, which is quite difficult with or without CPB. The use of BIS remains controversial. Monitoring anaesthetic

Table 1: Demographic distribution of patients

	Group 1	Group 2	P Values
Age (yrs)	44.15±11.29	45.15±11.46	0.783
Sex (M/F)	10/10	9/11	0.751
Weight(KGS)	53.59±12.01	52.68±11.55	0.808
Height (CM)	157.10±7.19	157.30±6.32	0.926
BSA(M2)	1.52±0.18	1.52±0.17	0.931

Table 2: Drug doses in mg on CPB

Drug	Isoflurane group		Conventional group		P value
	Mean	SD	Mean	SD	
Fenatanyl	0.94	0.12	0.88	0.10	0.100
Propofol	4.00	12.31	128.00	59.96	0.000*
Phenylephrine	0.40	0.38	0.09	0.16	0.002*
Midazolam	1.00	1.03	3.90	1.25	0.000*

* Statistically significant

Table 3: Comparison of Vasoactive inotrope score

Vasoactive Inotrope score	Isoflurane group		Conventional group		P value
	Mean	SD	Mean	SD	
Vasoactive Inotrope score	2.10	2.02	3.00	2.51	0.220

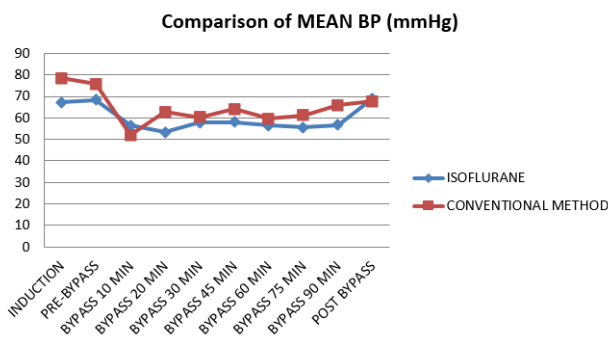


Fig. 2: Mean blood pressures

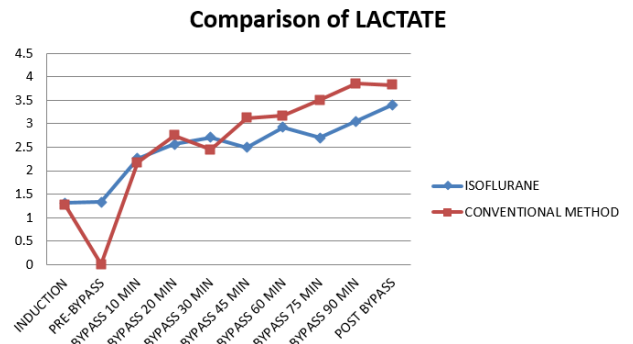


Fig. 4: Comparison of LACTATE

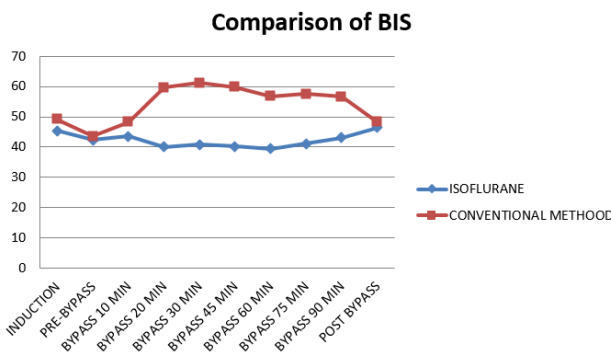


Fig. 3: Comparison of BIS

depth based on autonomic signs is challenging during CPB because these signs are largely absent. However, hypertension during normal CPB flows may indicate that anaesthetic depth or the degree of neuromuscular blockade is inadequate. In our study we found higher mean blood pressure in conventional group with higher BIS values indicating inadequate anaesthesia needing excessive doses of propofol to avoid awareness. Traditional methods of measuring ETAC (End tidal anaesthetic concentration) are also impractical because of the minimal blood flow through the lungs during CPB. Several studies suggest measuring the oxygenator membrane exhaust gas for halogenated anaesthetic as a surrogate for ETAC.⁹⁻¹² The BIS monitor is the only U.S. FDA approved monitor to assess the anaesthetic state of the central nervous system. However, its use during cardiac surgery and in

the general surgical population in preventing awareness is unreliable. Patients may report awareness, despite adequate BIS levels (<60).^{13–15} However, in the absence of effect-site concentration monitors or a surrogate such as ETAC, the BIS monitor may have applicability in potentially reducing the incidence of awareness.^{15–17} Our use of ETAC and BIS –demonstrated that the combination of ETAC and BIS facilitated maintenance of adequate level of anaesthesia and stable haemodynamics in isoflurane group.

When volatile anaesthetics are used, ETAC may be clinically useful during CPB. This is not routinely practiced despite being tested and advocated by many investigators, proving that monitoring of ETAC at the membrane exhaust port accurately reflects serum anaesthetic concentrations.^{11,12} The inability to relate the anti-ischemic effects of volatile anaesthetics to improvement of myocardial oxygen supply–demand balance led to the concept that these agents may have direct cardio-protective properties.¹⁸ Volatile anaesthetics have been shown to directly precondition^{19,20} or indirectly enhance IPC, resulting in cardio-protection against myocardial infarction with the KATP channel playing an important role.¹⁹ Pharmacological preconditioning produced by volatile agents, including isoflurane, desflurane, and sevoflurane, is remarkably similar to IPC and shares many of the same signal transduction elements. In our study we compared the inotropic score in both group and we observed that the requirement of inotropes and constrictors were significantly low in post operative period in isoflurane group indicating myocardial protective effect in isoflurane. In one study where they compared total intravenous anaesthesia (TIVA) with the use of volatile anaesthetic agents, such as isoflurane, for patients undergoing cardiac surgery found that the isoflurane group was associated with a lower mortality and incidence of adverse myocardial outcomes.^{21,22} As per one randomized controlled study of 320 elective CABG patients, in which 80 patients received propofol, 80 midazolam, 80 sevoflurane and 80 desflurane. All patients received a remifentanyl-based anaesthetic regimen. Postoperative troponin I and inotropic support was significantly lower in the volatile anaesthesia group. They concluded that a better preservation of early postoperative myocardial function with volatile anaesthetic agents resulted in a shorter ICU and hospital length of stay.²³ The blood lactate levels studied in our group show lower levels in the isoflurane group indicating improved tissue perfusion. However when on CPB our study shows higher use of phenylephrine in isoflurane group. This might be related to vasodilatory effect of isoflurane so the mean blood pressures were low in this group.

This study had some limitations. First this was a pilot project before the major trial can be conducted. Secondly the sample size was small so difficult to show statistical significance in few variables.

5. Conclusion

In conclusion, in patients undergoing heart surgery with CPB, the findings of this study indicate that appropriate use of isoflurane to maintained depth of anaesthesia during CPB should be monitored with use of BIS and ETAC. With use of isoflurane is associated with good myocardial protection, better maintenance of depth of anaesthesia and steady maintenance of haemodynamics.

6. Source of Funding

None.

7. Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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