

**COMPARISON OF TIVA VS INHALATIONAL MAINTANENCE OF
ANAESTHESIA FOR POST OPERATIVE DELIRIUM IN ADULT CABG
SURGERY:PROSPECTIVE RANDOMIZED SINGLE BLINDED STUDY**

Dr. VARSHA AV

DM CARDIOTHORACIC AND VASCULAR ANAESTHESIA THESIS

YEAR : 2020-2022



**SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND
TECHNOLOGY, TRIVANDRUM**

An Institution of National Importance established by an Act of the Indian Parliament (Act
No.52 of 1980)

Dept. of Science and Technology, Govt. of India
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A THESIS SUBMITTED BY

Dr. VARSHA AV

TO

**SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND
TECHNOLOGY, TRIVANDRUM**

IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE AWARD OF

DM CARDIOTHORACIC AND VASCULAR ANAESTHESIA

YEAR : 2020 - 2022

DECLARATION BY THE STUDENT

CERTIFICATE

I, Varsha AV hereby certify that I had personally carried out the work depicted in the thesis titled, "**Comparison of TIVA Vs inhalational maintenance of anaesthesia for post-operative delirium in adult CABG surgery: Prospective randomized single blinded study.**"

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Date 12/8/22.


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*Clearance was obtained from the Institutional Ethics Committee / Institutional Animal Ethics / Institutional Committee for Stem Cell Research / Other appropriate committees (if any, specify) for carrying out the study.

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LIST OF ABBREVIATIONS

1.	ABG	Arterial blood gas
2.	BIS	Bi-spectral index
3.	BMI	Body mass index
4.	CABG	Coronary Artery Bypass Surgery
5.	CAM-ICU	Confusion Assessment Methods- Intensive Care unit
6.	CPB	Cardiopulmonary bypass
7.	MMSE	Mini-mental status examination
8.	MoCA	Montreal Cognitive Assessment
9.	NIRS	Near Infrared spectroscopy
10.	POD	Post- operative day
11.	POCD	Post-operative cognitive dysfunction
12.	NCR	Neurocognitive recovery
13.	TEE	Transesophageal echocardiography
14.	TIVA	Total intravenous anaesthesia

SYNOPSIS

Introduction

Delirium and postoperative cognitive dysfunction (POCD) are major causes of morbidity after cardiac surgery. Anaesthetic agents can have both neuroprotective as well as neurotoxic properties and potentially have a role in pathogenesis of cognitive dysfunction. Recent studies have shown total intravenous anaesthesia (TIVA) with propofol to have lesser incidence of POCD when compared with inhalational maintenance of anaesthesia with sevoflurane in non-cardiac surgeries. However, there is scarce literature comparing these two agents in cardiac surgery despite the relatively high incidence of cognitive dysfunction in this group.

Objective

To compare the incidence of delirium and cognitive dysfunction (at one week) between TIVA and inhalational maintenance of anaesthesia in adult patients undergoing elective coronary artery bypass surgery (CABG) with cardiopulmonary bypass (CPB)

Methods

This was a prospective, randomised, single-blinded study. Adult patients (>18 years) undergoing elective CABG under CPB were randomised to receive either TIVA with propofol or inhalational maintenance of anaesthesia with sevoflurane. Anaesthetic depth was monitored to maintain bispectral index between 40-60. Delirium was assessed on post-operative days (POD) 1 and 2 using the Confusion-Assessment Method for the intensive care unit (CAM-ICU). The presence of "early POCD" was diagnosed when there was a reduction of more than 2 points in the Montreal Cognitive Assessment (MoCA) score compared to baseline. The baseline demographic and intraoperative variables were compared between the two groups. Chi-square and independent samples "t" test were used for categorical and continuous variables respectively. ANOVA test was used for intergroup comparisons.

Results

Seventy-two patients were included in the study and randomised to receive propofol (36) or sevoflurane (36) based anaesthesia. The mean age of the study population was 59.4 years (SD 8.6 years). All the baseline variables and intraoperative variables including atheroma grades, NIRS values, nadir hemoglobin, glycemic control and oxygenation were comparable between

the two groups. Fifteen (21.7%) patients in the cohort developed delirium and 31 (44.9%) patients had “early POCD”. The incidence of delirium was higher in the sevoflurane group (12, 34.2%) compared to the propofol group (3, 8.8%), OR 1.72 (95% CI: 1.13-2.62), p 0.027*. “Early POCD” was higher in sevoflurane (20, 57.1%) compared to propofol (11, 32.3%), OR 1.63 (95% CI: 1.01-2.62), p value 0.038*. In patients age more than 65 years, 7/ 11 (63.6%) patients who received sevoflurane developed delirium in contrast to propofol where only one of 7 (14.2%) patients developed delirium, p 0.03*.

Conclusion

Propofol based TIVA was associated with lesser incidence of delirium and cognitive dysfunction in our cohort. Sevoflurane can be preferably avoided in the elderly. The observations could be explained by the anti-inflammatory and antioxidant properties of propofol in addition to the neurotoxic effects of sevoflurane. Further large scale, multi-center, randomized trials with longer follow-up duration are needed to substantiate and analyze the long-term clinical relevance of this observation.



INTRODUCTION

Introduction

Delirium is a common neurologic complication after cardiac surgery. Estimates of the incidence have ranged from 26 to 52%¹ in various studies. The occurrence of postoperative delirium (POD) is associated with worse outcomes, including prolonged length of stay in the ICU and hospital, increased morbidity, mortality, compromised long-term cognitive function and physical ability, and elevated medical care costs.

Several factors including cerebral anoxia, embolism, excessive excitatory neurotransmitter release, systemic inflammatory response, electrolyte and metabolic disorders and hemodynamic changes have been demonstrated to contribute to postoperative neurological dysfunction and delirium.²⁻⁴ Previous studies have shown that inhalation anaesthesia and total intravenous anaesthesia (TIVA) may produce different degrees of cerebral protection in these patients. Observations from studies in both non-cardiac and cardiac surgical cases have shown conflicting reports. Effects of these two types of anaesthesia in cardiac surgery with cardiopulmonary bypass (CPB) also remain controversial and much debated.

Propofol is a well-known potentiator of GABA receptors. It reduces cerebrovascular resistance, cerebral blood flow (CBF) and cerebral oxygen delivery during CPB but maintains cerebral autoregulation. Propofol being a free radical scavenger may reduce the burst of reactive oxygen species occurring with reperfusion and reduce mitochondrial damage and cell injury.⁵ Sevoflurane has been postulated to have an important role in cardio-protection (and neuroprotection) by mechanisms of conditioning in vitro. However, these observations have seldom translated into clinical benefits in various prospective studies.

A recent meta-analysis comparing propofol to inhalational agents in elderly patients undergoing non-cardiac surgeries concluded that there was moderate evidence in favour of propofol use with respect to reduction in postoperative cognitive decline.⁶ There is limited literature regarding the cognitive effects of propofol versus sevoflurane in cardiac surgery. Moreover, some of the available studies have had confounders such as baseline cognitive impairment, perioperative oxygen desaturations and have differed with respect to methods as well as timing of cognitive assessments.

It remains a fact that occurrence of delirium and postoperative cognitive dysfunction (POCD) is not necessarily related to the use of the anaesthetic agent alone. Several other factors such as oxygenation, temperature management, glycaemic control, heart rate control and management of blood loss and coagulopathy remain integral to optimal post-operative outcomes. Any aberrations in these factors have the potential to confound the observations of prospective studies. In view of these considerations, well conducted clinical trials recruiting homogenous cohorts and having standardised management protocols might have a significant role in providing further insights regarding the choice of anaesthetic agent with the least propensity to cause delirium and POCD.

There is a need for prospective randomised studies especially in the Indian setting to address these scientific queries.

The goal of the present study is to determine the incidence of early post-operative delirium and changes in cerebral oxygen saturations in TIVA vs the inhalational anaesthesia maintenance group in a cohort of patients undergoing coronary artery bypass surgery (CABG) under CPB in a tertiary care centre in south India.



AIMS AND OBJECTIVES

Hypothesis

We hypothesised that TIVA during CPB would reduce the incidence of early postoperative delirium in patients undergoing CABG with CPB as compared to inhalational anaesthesia maintenance.

Aim

To determine the incidence of early post-operative delirium and changes in cerebral oxygen saturations in TIVA compared to the inhalational anaesthesia maintenance group in a cohort of patients undergoing CABG under CPB in a tertiary care referral hospital in south India.

Objectives

Primary objectives

1. Compare the incidence of early postoperative delirium in both the groups.
2. Compare the incidence of early post-operative cognitive dysfunction in both the groups.

Secondary objectives

1. Compare the cerebral oxygen saturation in both the groups
2. To analyse the risk factors for delirium and POCD in the cohort
3. To analyse the glycaemic control in both the groups



REVIEW OF LITERATURE

Literature Review

Problem Statement: Post-operative cognitive Dysfunction

Delirium, delayed neurocognitive recovery and post-operative cognitive dysfunction (POCD) have been closely associated with anaesthesia and both cardiac and non-cardiac surgeries. In addition to short term consequences such as prolonged intensive care unit (ICU) stay, hospitalization, higher morbidity, these cognitive problems can have potential long-term implications which include loss of vocation, financial and social dependence. Delirium is quite common and some studies have quoted an incidence of nearly 53.5% after cardiac surgery.⁷ The incidence of POCD can be as high as 25-40% in the first week after surgery. This reduces to 10% at the end of one week and 1% at 3 months after the surgery.⁸ The first report of cognitive dysfunction after surgery was nearly 125 years ago by George Savage. He aptly titled the presentation as “Insanity following the use of Anaesthetics in Operations”.⁹ The first report of cognitive changes after cardiac surgery emerged in the 1960s.¹⁰ The incidence of cognitive dysfunction was reported as higher in cardiac surgery (up to 79%) especially with cardiopulmonary bypass (CPB) compared to the other surgeries¹¹. Bedford reported that the previously normal elderly people who underwent anaesthesia developed forgetfulness and impaired directional function.¹² The risk of cognitive dysfunction after non-cardiac surgeries was also described in the subsequent years.

A landmark prospective study compared the incidence of POCD in patients undergoing different types of surgery and anaesthesia.¹³ The procedures included light sedation (coronary angiography), general anaesthesia (non-cardiac surgery, hip joint replacement) and general anaesthesia for cardiac surgery (coronary artery bypass grafting [CABG] with CPB). The incidence of POCD at day 7 was 43% in the CABG group vs 17% in the hip replacement group. However, there were no differences between the three groups in the POCD at 3 months indicating that overall POCD was independent of the anaesthesia or surgery. Cognitive decline after cardiac surgery has been reported to be around 24% at 6 months and 42% at 5 years based on systematic studies.¹⁴

Classification

The spectrum of cognitive dysfunction after surgery includes delirium and POCD. Based on temporal evolution, different terminologies are used. Delirium usually lasts 24-72 hours. POCD is described to be present when there is cognitive dysfunction 30-days after surgery. Often, the term “delayed neurocognitive recovery (NCR)” is used when there is cognitive dysfunction between 7-30 days after the surgery (interchangeably used with “early POCD”, POCD at 1-week etc). The “30-day duration” for POCD has been included to avoid the risk of confounding factors such as postoperative pain, concomitant medicine use, immobility, lack of sleep and emotional stress. The term POCD can be used to describe cognitive dysfunction after surgery for up to 1 year following surgery. Cognitive dysfunction persisting after a year following surgery is termed “Neurocognitive Dysfunction” (NCD). The term “Perioperative Neurocognitive Disorders” has been recommended by the “The Nomenclature Consensus Working Group” to address all the above-mentioned disorders.¹⁵

Operational definitions for Delirium and POCD

“Delirium is an acute state of confusion and inattention, which may be accompanied by an altered level of consciousness and disorganized thinking”.¹⁶ Delirium has various components as described in the Diagnostic and Statistical Manual, 5th edition (DSM-5).¹⁷ These include disturbances in attention and awareness, rapid onset, acute distress, cognitive dysfunction, and abnormalities not explained by any other disorder. There should be no evidence of any direct medical condition or drug effect/ withdrawal. Post-operative delirium usually occurs within one week (often 24-72 hours) after surgery and can occur till the time of hospital discharge.

Patients with post-operative delirium following cardiac surgery are at increased risk (14 times higher risk) for neurocognitive dysfunction at one week following cardiac surgery compared to non-surgical controls.¹⁸ Risk factors for delirium include advanced age, pre-existing cognitive impairment, depression, diabetes mellitus, comorbidities, frailty, emergency surgery, excessive pain, poor functional status and prolonged ICU stay.¹⁹

POCD is defined to be present when there are abnormalities in various cognitive domains which include memory, executive function, visuo-spatial orientation, and language. Usually, POCD is short-lasting. Often, POCD manifests as minor impairments in one or more cognitive domains and as a result is under-diagnosed. Prevention and early diagnosis of POCD is important as it interferes with quality of life if persistent long-term. The variable incidence of POCD in literature is due to different assessment methods used. The final verdict on whether delirium and POCD are part of the same spectrum or different disease processes per se is a matter of contention.

Assessment Methods

The “Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)” is one of the most common assessment techniques used for screening delirium. This is applicable and designed for use in the intubated patients. The four core features include acute onset or fluctuating course, inattention, disorganized thinking and altered consciousness level. Individual items are categorized as absent/ present. CAM-ICU is considered positive when three out of four features are present. Validated Hindi and Malayalam versions are available in addition to the English for cross-cultural adaptation. The CAM-ICU assessment method has got a high sensitivity (93-100%), specificity (98-100%) and high inter-rater reliability.²⁰ The CAM-ICU version has been provided in the appendix.

The Montreal Cognitive Assessment (MoCA) scale is a validated assessment tool for detection of delayed neurocognitive recovery (NCR) or POCD in the post-operative setting. MoCA (30-score instrument) covers short term memory, visuo-spatial functions, execution, attention, concentration, working memory, language, and orientation. It has higher inter-rater reliability. A change in MoCA score of 3 scores from baseline has high specificity (88%) and sensitivity (78%) for detection of NCR.²¹ A change in MoCA score by 2 points has a lesser specificity (82%) with a marginally better sensitivity (82%). Other options for assessing decline compared to baseline include cut-off scores less than 26 and a decline by more than one standard deviation compared to baseline. MoCA score has a validated Malayalam version for cross-cultural adaptation.²² The MoCA score version has been attached in the appendix.

Mechanisms of delirium and POCD after cardiac surgery

(A) Inflammation

There is a proinflammatory and prothrombotic state which gets activated following a CABG. This systemic inflammatory response lasts for a few days following cardiac surgery. The proinflammatory cytokines involved include interleukins 6, 8, tumour necrosis factor (TNF)- α , and damage associated molecular molecules such as high mobility group box-1 (HMGB1), and S100 calcium binding proteins^{23,24}. The inflammatory response occurs due to contact activation of immune mediators to foreign surfaces, ischemia-reperfusion injury to major organs, endotoxemia and leucocyte/ platelet activation, all of which occur during CPB.^{25,26} The inflammation also causes disruption of the blood brain barrier and resultant neuroinflammation.²⁷ This neuronal damage could result in cognitive impairment. Similar systemic inflammatory responses can occur after off-pump CABG as well.²⁸

Other contributing factors to inflammation include anaesthetic agents (described later), opioids, heparin, and median sternotomy. Polymorphisms in multiple genes which influence inflammatory responses are associated with an elevated risk of developing neurocognitive dysfunction after surgery. These polymorphisms include those in the *CRP*, *SELP*, *GPIIIA*, and *iNOS* genes.²³

(B) Embolism

Micro emboli following aortic manipulation and resultant plaque disruption could lead to ischemia in strategic brain lesions. The resultant diaschisis may manifest as neurocognitive dysfunction especially in the elderly.²⁹ Atheroma burden monitoring of the aorta by transoesophageal echocardiography and monitoring for micro emboli by transcranial doppler are useful strategies to ascertain the role of atherosclerotic burden and embolization in cognitive dysfunction following cardiac surgery.

(C) Cerebral Autoregulation

Altered cerebral blood flow both above and below the target mean arterial pressure (MAP, ideally 60 mm of Hg, lower limit 45-80 mm Hg) have been associated with delirium and POCD. Higher blood pressure excursions above the autoregulation range can lead to delirium.³⁰ Lower MAP values have been shown to be associated with neuronal injury, increased glial fibrillary acidic protein (GFAP), cerebral venous oxygen desaturation and POCD.³¹

(D) Temperature Management

Hypothermia reduces cerebral metabolic rate especially during times of reduced perfusion and helps neuronal injury and POCD. Rewarming to a lower temperature (34⁰ Celsius compared to 37⁰ Celsius) is associated with a lower risk of cognitive dysfunction one week after cardiac surgery.³²

(E) Glucose control

Fluctuations in glucose and hyperglycaemia have been associated with higher risk of POCD especially in non-diabetic subjects.³³ Diabetic subjects have chronic compensatory mechanisms and are less susceptible to neuronal injury secondary to minor blood sugar fluctuations.

(F) Anaesthesia and POCD

The neurotoxic as well as neuroprotective mechanisms of inhalational anaesthetic agents and propofol have been discussed in literature. Propofol and volatile anaesthetics such as sevoflurane, isoflurane and desflurane increase GABA-A receptor function. Mechanisms implicated regarding anaesthetic use and POCD include

- (i) increased GABA mediated amyloid and tau pathology,

- (ii) disruption of gamma oscillation patterns usually associated with clearance of amyloid beta,
- (iii) anaesthetic drug induced neuroinflammation, and
- (iv) direct neuronal damage²³

Increased phosphorylation of tau with aggregation and amyloid beta-oligomerization have been described with volatile anaesthetic agents.³⁴ Changes in cerebrospinal fluid levels of amyloid beta and tau have been described post cardiac surgery. Isoflurane has especially been suspected to accelerate Alzheimer's disease pathology. Propofol has been postulated to attenuate isoflurane induced caspase 3 activation and amyloid beta oligomerization.³⁵ However, most of these observations have been from animal models and patient data is hardly available. The clinical correlates of these pathologies also need to be elucidated.

Anaesthetic administration using bispectral index (BIS) titration can potentially reduce POCD.³⁶ There has been as much as 40% decrement in the incidence of cognitive dysfunction with a BIS-guided 30% reduction in mean end-tidal inhaled anaesthetic.³⁷

The concept of anaesthetic pre- and post-conditioning has been described with volatile anaesthetics. Ischemic preconditioning by inhalational anaesthetics has been shown to reduce ischemia-reperfusion injury in animal models.³⁸ Pre-treatment with isoflurane has been shown to reduce infarct size and provide neuroprotection via increased inducible NO synthase.³⁹ Sevoflurane has also been shown to precondition the brain to ischemia and inflammation in animal.⁴⁰ However, none of the hypothesis has been conclusively proven in human studies.

Propofol is a short acting anaesthetic agent and has been shown to have multimodal neuroprotection in various neuronal injury models.⁴¹ Propofol activates the GABA receptor and modulates the excitatory amino acid transmitter system. Propofol can scavenge reactive oxygen species and reduce oxidative stress by reducing free radical generation.⁴² Propofol has been shown to reduce glutamate mediated excitotoxicity and NMDA-receptor mediated calcium increase.⁴³ Propofol has been shown to have a role in reducing neuronal apoptosis.⁴⁴ Anti-inflammatory effects and downregulation of aquaporin-4 also aid in neuroprotection.⁴¹

The balance between neurotoxicity and neuroprotection offered by both the inhalational anaesthetics and propofol depends on the concentration, dose, and timing of use. Hence, the observations from pre-clinical studies need not always translate into benefits in human studies.

Clinical studies comparing Propofol and Sevoflurane (inhalational anaesthesia)

The main goals while choosing an appropriate anaesthetic agent for CABG include to reduce myocardial as well as other major organ injury such as neuronal damage. The anaesthetic preconditioning concept mentioned with volatile anaesthetics and their beneficial effect in ameliorating reperfusion injury in animal models can be considered a breakthrough. The mechanisms include activation of potassium activated ATP channels and inhibition of the opening of the mitochondrial permeability transition pore (mPTP).^{45,46} However, these observations of possible cardioprotective effects have not completely translated into remarkable benefits when compared to other agents such as propofol in clinical trials.

A few randomized trials and meta-analysis reported benefit of sevoflurane compared to propofol in reducing cardiac biomarkers, myocardial injury and one year mortality after CABG.^{47,48,49,50} On the contrary some of the randomized trials have failed to show any mortality benefit.^{51,52} Subsequently, a large landmark clinical trial involving 5400 patients (MYRIAD trial) failed to show any mortality benefit when comparing inhalational anaesthetic to propofol in elective CABG.⁵³ An updated meta-analysis concluded that there was no significant difference between the inhalational agents and propofol with regards to lower mortality or post-operative safety outcomes.⁵⁴ There were 8 trials assessing POCD and 3 trials assessing delirium in this meta-analysis. There was no statistically significant difference between the volatile anaesthetics and TIVA groups in the incidence of delirium (RR = 0.96, 95% CI: 0.71–1.29, p = 0.78), without heterogeneity. There was no statistically significant difference between the volatile anaesthetics and TIVA groups in the incidence of postoperative cognitive impairment (RR = 1.20, 95% CI: 0.74–1.94, p = 0.46), with moderate heterogeneity ($I^2 = 59\%$).

A Cochrane meta-analysis of 28 randomized trials including 4507 elderly patients undergoing different non-cardiac surgeries concluded that there was only low certainty evidence regarding the fact that propofol based anaesthesia could have lower incidence of POCD compared to inhalational anaesthesia⁵⁵. As expected, further analysis regarding important data such as intraoperative hypotension and duration of ICU stay could not be performed due to the heterogeneity of the studies. A subsequent recent meta-analysis comprising 15 randomized trials with 1852 patients undergoing non-cardiac surgery concluded that there was moderate evidence to show that propofol based anaesthesia is associated with a lower incidence of POCD in elderly non-cardiac surgical patients⁶. There was also low-level evidence to show that propofol based anaesthesia is associated with a lower level of inflammation.⁶ S-100 B protein (which is a biomarker of acute brain injury) was lower after propofol. The difference in POCD was different between the two groups on POD 2-6. There was some heterogeneity in view of the different assessment methods used. The levels of TNF alpha and IL-6 were reduced in the propofol group on POD 1. It is possible that the higher levels of pro inflammatory cytokines could have resulted in a higher neuroinflammation and cognitive dysfunction in the inhalational anaesthesia group

A detailed description of the various studies which have addressed the differences between inhalational agents and propofol in the context of post-operative cognitive outcomes has been mentioned in Tables 1 and 2 given below.

Table 1 : Studies comparing propofol based anaesthesia with inhalational agents in adult surgeries

Trial	Comparison	Outcome measures	Results of the study	Discussion
Tang et al 2014 ⁵⁶ Elderly > 60 years Radical rectal resection	Sevoflurane (99) versus propofol (101)	Detailed neuropsychological battery of tests	No significant difference in POCD at day 7 between the two groups: propofol (33.3%) and sevoflurane (29.7%), however, sevoflurane associated with greater cognitive decline in elderly with MCI	Higher depth of anaesthesia and BIS was maintained 30-60 Patients with MCI also included Severe POCD higher in sevoflurane 16.1% compared to propofol (6.1%), p 0.01
Mei et al (2020) ⁵⁷ Elderly, hip, and knee replacement	Sevoflurane (103) versus propofol (106)	Post-operative delirium on day 1,2,3 by CAM method	postoperative delirium (days 1,2,3) 33.0% with propofol and 23.3% with sevoflurane (<i>P</i> = 0.119) Days of POD higher in propofol (p 0.049), no significant difference in severity	baseline MMSE of more than 24 were included use of midazolam might have been a confounder propofol has a longer elimination time and hence possibly longer duration of delirium

<p>Nishikawa et al, 2004 ⁵⁸</p> <p>Elderly > 65 years</p> <p>Long duration laparoscopic surgery</p>	<p>Propofol (25) versus sevoflurane (25)</p>	<p>Post-operative delirium on the first 3 days by Delirium Rating Scale (DRS)</p>	<p>No difference in the incidence of post-operative delirium between the two groups</p> <p>DRS scores higher in the propofol group compared to sevoflurane (p < 0.01)</p> <p>Emergence after anaesthesia faster with sevoflurane (p < 0.01)</p>	<p>Depth of anaesthesia was not monitored</p> <p>Higher doses of propofol were administered</p> <p>Post-operative pain scores were comparable</p>
<p>Kalimeris et al, 2013 ⁵⁹</p> <p>Carotid endarterectomy</p>	<p>Propofol (23) versus sevoflurane (21)</p>	<p>MMSE at one hour and after 24 hours of surgery</p> <p>Blood lactate, S100B and P selectin analysed</p> <p>Antioxidative markers malondialdehyde/low-density lipoprotein ratio and nitrate þ nitrite concentrations</p>	<p>Cognitive impairment lesser in propofol (13%) compared to sevoflurane (43%), p < 0.05.</p> <p>Lower lactate, S 100 B and oxidative stress markers lower with propofol</p>	<p>Small sample size</p> <p>Cerebral blood flow assessment not done</p>
<p>Shin et al, 2021 ⁶⁰</p> <p>Retrospective study</p> <p>Cardiac surgery with CPB</p>	<p>Sevoflurane with dexmedetomidine (340 patients)</p> <p>Versus Propofol (194 patients)</p>	<p>Post-operative delirium using CAM-ICU score</p> <p>Propensity matched analysis</p>	<p>No significant difference between the two groups</p> <p>6.2% in sevoflurane compared to 10.8% in propofol</p> <p>Hyperactive delirium lesser in sevoflurane-dexmedetomidine group</p>	<p>Retrospective study</p> <p>Possible that hypoactive delirium might have been missed</p> <p>Use of dexmedetomidine in sevoflurane group could have confounded the incidence of delirium with sevoflurane as the former is known to reduce hyperactive delirium</p>

			Older age, emergency surgery and lower preoperative albumin associated with higher risk of delirium	
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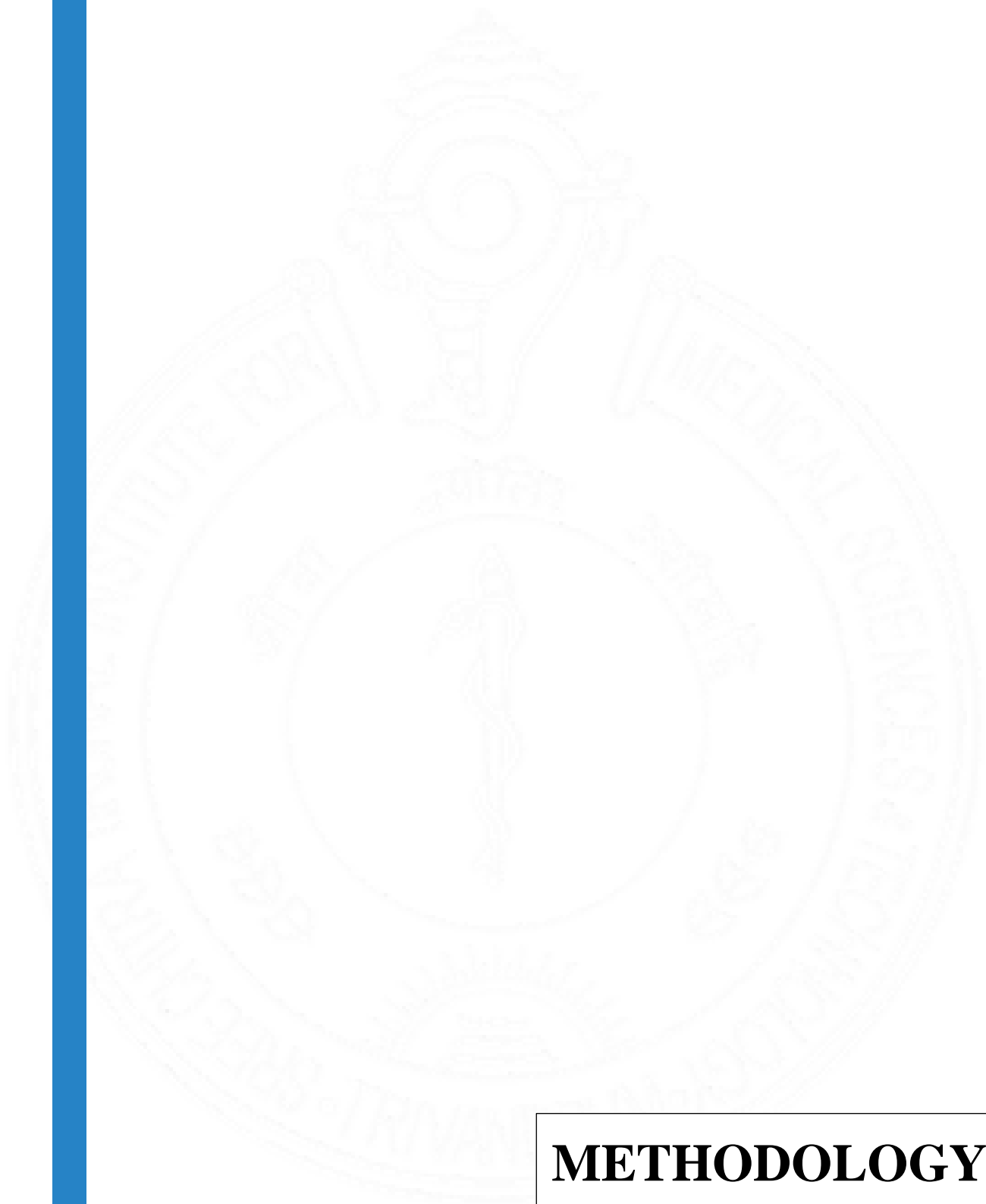
Trials	Comparisons	Outcome measures	Results	Discussion
Ishii et al, 2016 ⁶¹ Elderly > 70 years undergoing gastrectomy, colectomy or resection	Sevoflurane (30) versus propofol (29)	Post-operative delirium assessed by CAM method	Propofol (6.9%) group had lesser incidence of delirium compared to sevoflurane (26.7%), p 0.038	Faster emergence times and fewer adverse events lead to lesser delirium in the propofol group
Geng et al, 2017 ⁶² Elderly > 65 years Laparoscopic cholecystectomy	Propofol (50), sevoflurane (50) and isoflurane (50)	POCD at POD 1 and POD 3 S100beta and inflammatory cytokine profile POCD assessed using psychometric and neurocognitive tests	POCD (day 1 and day 3) significantly lesser in the propofol group (10%, 4%) compared to sevoflurane (30%, 20%) (p 0.012, 0.013) and isoflurane (50%, 30%) POCD lesser in sevoflurane compared to isoflurane Plasma concentration of S100 beta, AB1-40, and inflammatory	Long term outcomes not assessed Sample size small and single site, so findings may not be generalizable

			cytokines lesser in propofol and sevoflurane compared to isoflurane	
Qiao et al, 2015 ⁶³ Oesophageal carcinoma resection Elderly 65-75 years	Sevoflurane (30), sevoflurane with methylprednisolone (30) and propofol (30)	MMSE and MOCA on POD 1, 3 and 7 S100beta and inflammatory markers on POD 1,3 and 7	Higher POCD (p 0.015*) and inflammatory markers in the sevoflurane group compared to placebo	Perioperative methylprednisolone before sevoflurane helped in reducing POCD in the sevoflurane with methylprednisolone group
Zhang et al, 2018 ⁶⁴ Elderly > 65 years Cancer surgery	Sevoflurane (196) versus propofol (196)	Detailed neuropsychological battery with 7 tests and 9 subscales	Delayed neurocognitive recovery lower in the propofol (14.8%) group compared to sevoflurane (23.2%), p 0.038 Good pain relief in the propofol group	A control group was included which had a delayed neurocognitive recovery of 6.8%, shows that the tests can have a false positive value Large sample size

Take home messages from the literature review:

1. Neurocognitive dysfunction is relatively common after cardiac surgery and associated with potential morbidity and economic burden.
2. The spectrum of cognitive dysfunction varies from delirium, delayed neurocognitive recovery to POCD.
3. Use of proper assessment tools is paramount for correctly diagnosing delirium and POCD.
4. Both sevoflurane and propofol have neuroprotective as well as neurotoxic properties. The evidence of ischemic preconditioning demonstrated in preclinical studies of sevoflurane has not been conclusively demonstrated in clinical trials
5. There is moderate level of evidence to suggest that propofol based anaesthesia is associated with a lower incidence of POCD compared to inhalational agents in patients (elderly patients) undergoing non-cardiac surgery.

Clinical trials comparing the cognitive outcomes between propofol and sevoflurane in cardiac surgery (such as CABG) with CPB are limited even though the incidence of POCD may be higher in this subset compared to non-cardiac surgery



METHODOLOGY

Methods

Study Design

It was a prospective, randomized, single-blinded interventional study.

Setting

Tertiary care referral hospital in south India.

Prior approval was obtained from the Technical Advisory Committee and the Institutional Ethics Committee. Primary investigator (Observer 1) examined all the patients preoperatively and verified inclusion and exclusion criteria (vide infra). A written informed consent for the study and anaesthesia was taken from all the patients. The trial was registered in the Clinical Trials registry CTRI/2021/03/032265

Rationale for patient selection:

Postoperative delirium is more common in patients with atherosclerotic disease and coronary artery disease has an atherosclerotic pathology. Hence, the study cohort was chosen to represent patients with coronary artery disease undergoing elective CABG under CPB.

Inclusion criteria:

1. Age from 18 -80 years
2. Undergoing CABG on CPB
3. Consenting for the study

Exclusion Criteria:

1. Emergency surgery

2. Known allergy to components of anaesthesia
3. Hemodynamically significant stenosis of carotid arteries
4. Parkinson's disease or other neurological diseases
5. Poor language comprehension
6. Preoperative Medications: anticholinergics, antidepressants, antiepileptics, antiparkinsonian, drugs

Recruitment:

The principal investigator was responsible for recruiting patients. Patients were evaluated in the preoperative anaesthetic examination to determine eligibility (as per inclusion/exclusion criteria). If deemed eligible, patients were informed about the study and consent was obtained.

Randomization and blinding:

Computer generated random table were used to allocate subjects to one of the study groups. Sequentially numbered sealed opaque envelopes which contained the treatment allocation code were opened in the morning of surgery. Patients were unaware of group assignment. All the statistical analyses were performed by the biostatistician not involved in treatment allocation.

Study methods:

Baseline demographics of all the patients including age, sex, height, weight, body mass index (BMI), comorbidities and type of surgery were noted. Baseline MOCA score (appendix, English, and validated Malayalam version) was assessed the day before surgery.

Standard anaesthesia induction and intubation was done using fentanyl 5-10 mcg/kg, midazolam 0.05-0.1 mg/kg, propofol dose up to 2mg/kg and pancuronium 0.1mg/kg.

Fentanyl infusion was started at 2mcg/kg/hr. Standard ASA monitoring including electrocardiogram, blood pressure monitoring using invasive arterial lines and pulse oximetry were established once the patient was shifted inside the operation theatre and baseline vitals were recorded. Additionally, bispectral index (BIS) monitoring was done to ensure adequate depth of anaesthesia and maintained at 40-60. Near infrared spectroscopy (NIRS) to record cerebral oximetry and transoesophageal (TEE) for regular cardiac evaluation and to look for atheroma and its grade were used.

Patients in the TIVA group received propofol titrated to BIS for maintenance along with fentanyl infusion while the patients in the inhalational group received sevoflurane titrated to BIS along with fentanyl infusion for maintenance. The depth of anaesthesia was monitored and maintained in both the groups using BIS monitor. All patients were screened for presence of atheromatous plaque in the aorta and the Katz grading was noted.

CPB was instituted and maintained as per standard protocol. The mean arterial pressure (MAP) was maintained > 60mm Hg on CPB. Hypotension (defined as a MAP of < 60 mm Hg) was treated with Noradrenaline infusion and hypertension (defined as MAP >80 mm Hg) on CPB treated with NTG infusion after ensuring adequate depth of anaesthesia and analgesia. PaCO₂ was maintained at 35-45 mmHg. NIRS values were recorded at various time intervals: baseline, intubation, after going on CPB, after cross-clamping, at lowest temperature 30°C, after rewarming at 36°C, post-bypass and after skin closure. Hyperthermia during rewarming was avoided. Haematocrit was maintained >24 % on CPB. Other parameters recorded included duration of CPB, cross clamp time and intraoperative glucose levels.

After the surgery, patients were shifted to the intensive care unit (ICU). In the ICU, time to extubation readiness was noted. Dexmedetomidine infusion for sedation at 0.1 -0.3 mcg/kg /hour was started for all patients on arrival to the ICU as per institutional protocol. Fentanyl infusion at 0.5 to 1mcg/kg/hr was continued in ICU for analgesia. The vasoactive-ionotropic score was calculated from summing the maximum dose rates (after using correction factors for differential units of measurement) of inotropes and vasopressors which were administered during the first 24 hours after cardiac surgery. All patients received 6th hourly intravenous paracetamol for post-operative analgesia.

Monitoring for postoperative delirium (time frame: 48 hours after surgery) was done using Confusion Assessment Method for the ICU (CAM-ICU, appendix) on post-operative day (POD) 1 and 2 by the principal investigator. The CAM-ICU delirium severity assessment was performed twice daily (8am-4pm) on the first and second PODs. Monitoring for early postoperative cognitive dysfunction (Time Frame: at 7 days after surgery) was done using Montreal Cognitive Assessment (MoCA) to detect cognitive dysfunction. The change in MOCA score compared to baseline was noted. Duration of ICU stay, and hospital stay after surgery was also recorded.

Katz grading for atheroma

- Grade 1: normal-appearing intima of the aorta**
- Grade 2: extensive intimal thickening**
- Grade 3: sessile atheroma protruding <5 mm into the aorta**
- Grade 4: atheroma protruding >5 mm**
- Grade 5: mobile atheroma**

CAM-ICU scale for delirium: appendix

MOCA score: appendix

Vasopressor-inotropic score = (VIS=dopamine dose [$\mu\text{g kg}^{-1} \text{min}^{-1}$]+dobutamine [$\mu\text{g kg}^{-1} \text{min}^{-1}$]+100 \times epinephrine dose [$\mu\text{g kg}^{-1} \text{min}^{-1}$]+50 \times levosimendan dose [$\mu\text{g kg}^{-1} \text{min}^{-1}$]+10 \times milrinone dose [$\mu\text{g kg}^{-1} \text{min}^{-1}$]+10 000 \times vasopressin [units $\text{kg}^{-1} \text{min}^{-1}$]+100 \times norepinephrine dose [$\mu\text{g kg}^{-1} \text{min}^{-1}$]) using the maximum dosing rates of vasoactive and inotropic medications ($\mu\text{g kg}^{-1} \text{min}^{-1}$ or IU $\text{kg}^{-1} \text{min}^{-1}$) during the first 24 h after postoperative ICU admission

The demographic parameters included age, sex, height, weight, BMI, presence of comorbidities such as diabetes mellitus and hypertension, the Katz grade for atheroma in the

ascending aorta, arch of aorta and descending aorta, the CPB time and the aortic cross clamp time.

The arterial blood gas (ABG) at baseline, on CPB and post CPB were noted. The ABG parameters included pH, PO₂, PCO₂, bicarbonate, calcium, sodium, potassium, and haemoglobin.

The blood sugars were noted at baseline, on CPB and post CPB.

Outcome measures

Primary outcomes

Post-operative delirium (POD) was defined by the fulfilment of the CAM – ICU criteria which included 1) acute onset and fluctuating symptoms, 2) inattention, and either 3) an altered level of consciousness or 4) disorganized thinking.

Post-operative cognitive dysfunction (POCD) was defined as a reduction in MOCA score by more than 2 points compared to baseline. Assessment for early POCD was done on POD 7.

Secondary outcomes

Cerebral oxygen saturation: The NIRS values at baseline, intubation, on CPB, cross clamp, moderate hypothermia, rewarming, after CPB and after sternal closure were noted.

Glycaemic control: The blood sugars were noted at baseline, on CPB and post CPB.

The Katz grade for atheroma in the ascending aorta, arch of aorta and descending aorta were measured and compared between the treatment allocation groups as well as the group with post-operative delirium.

The nadir values of Hb, NIRS and PO₂ were noted.

Statistics

Sample Size calculation

Sample size calculation based on the previous study by Ishii K et al where they found the incidence of postoperative delirium 6.9% in propofol group and 32% in sevoflurane group.

Formula applied for sample size calculation:

$$n = [(Z_{\alpha/2} + Z_{\beta})^2 \times \{(p_1 (1-p_1) + (p_2 (1-p_2)))\}] / (p_1 - p_2)^2$$

where

$Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (for a confidence level of 95%, α is 0.05 and the critical value is 1.96)

Z_{β} is the critical value of the Normal distribution at β (for a power of 80%, β is 0.2 and the critical value is 0.84)

p_1 and p_2 are the expected sample proportions of the two groups.

36 subjects are needed in each group for a confidence interval of 95% and power of study 80%

Statistical Analysis

The study data was analysed using SPSS version 21(IBM) for Windows.

All baseline characteristics were tested for comparability among the two groups

Categorical data was presented as number (proportion/percentage) and analysed using Chi-square test. The data analysed using

Chi-square test included:

1. Comparison of proportion of male/ female, patients with comorbidities between the two groups and in those with delirium
2. Comparison of proportion with different Katz grades of atheroma between the two groups and in those with delirium

3. Comparison of proportion with post-operative delirium between the two groups
4. Comparison of proportion with post-operative cognitive dysfunction (early) between the two groups
5. Comparison of proportion of patients who were elderly (> 60 years) and who had post-operative delirium and POCD between the two groups

Student t test was used to detect statistically significant differences in means among the two groups. Mann Whitney test was used for non-parametric variables. ANOVA was used when appropriate for intergroup comparisons among the groups with/ without delirium with sevoflurane and propofol

The continuous variables analysed included

1. Demographic variables including age, BMI, CPB time and cross clamp time
2. The cerebral oximetry data including NIRS values at baseline, intubation, on CPB, cross clamp, moderate hypothermia, rewarming, after CPB and after sternal closure between the two groups
3. The ABG parameter values at baseline, during CPB and post CPB between the two groups
4. The blood sugars at baseline, on CPB and post CPB between the two groups
5. The comparison of MOCA scores at baseline and on post-operative day 7 between the two groups.
6. The comparison of nadir Hb, pO₂ and NIRS values between the two groups and those with delirium.

A p value of less than 0.05 was considered statistically significant.



RESULTS

Results

Consort statement

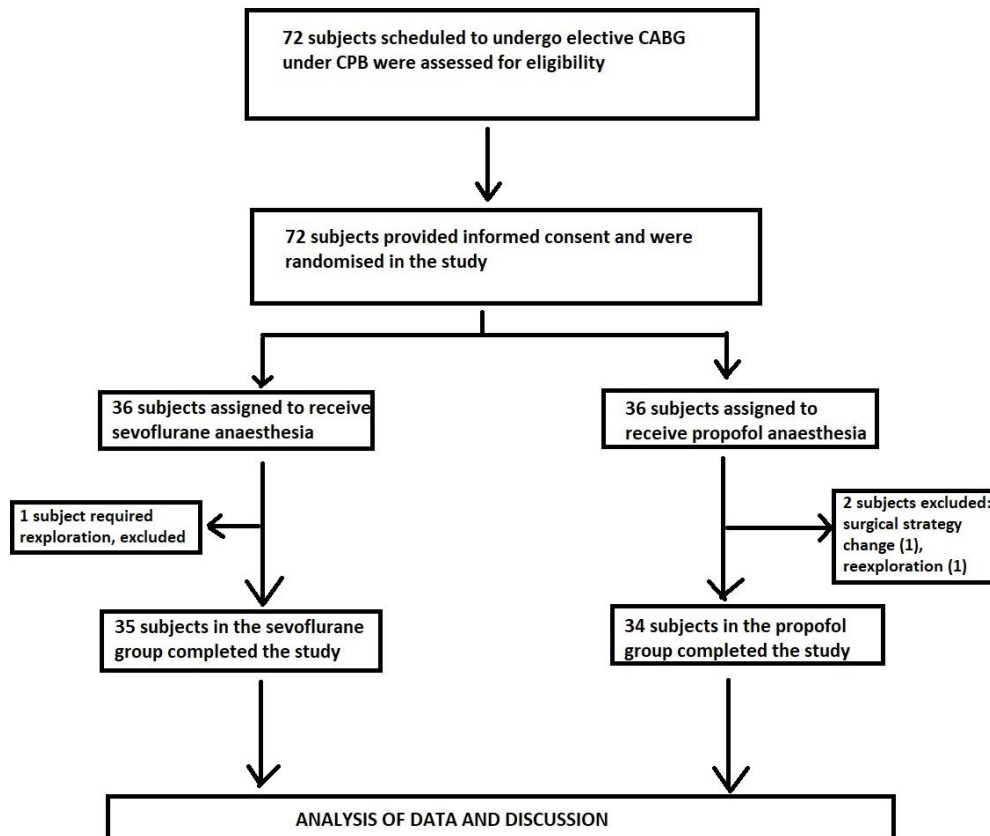


Figure 1: Consort diagram

A total of 72 patients were included and 36 patients were randomized to receive sevoflurane or propofol respectively. One patient in the sevoflurane group and 2 patients in the propofol group were excluded as 2 underwent re-exploration and 1 was operated off bypass.

The mean age of the study population was 59.4 years (SD 8.6 years), IQR 55-66 years.

There were 58 males (84.1%) and 11 females (15.9 %). The mean BMI was 25.84 (SD 3.85).

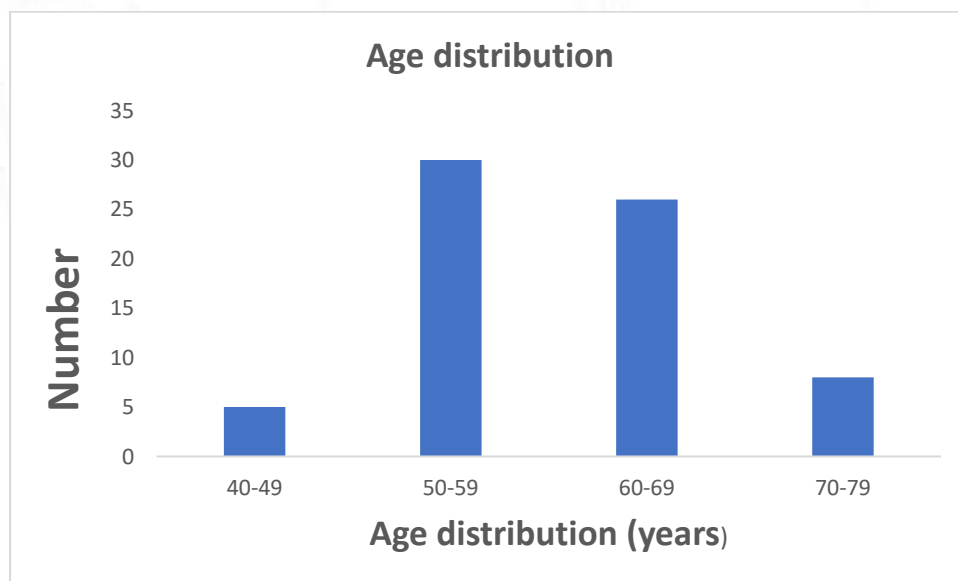
Diabetes mellitus was present in 49 (71%) patients and hypertension in 36 (52.2%) patients.

The mean CPB time was 131.76 (38.14) minutes. The mean cross clamp time was 69.03 (23.30) minutes.

Eight patients were 40-49 years (11.5%), 30 patients 50-59 years (43.47%) and 34 patients (49.3%) were older than 60 years of which 18 (26.1 %) were older than 65 years in the cohort.

The age distribution of the cohort is as shown in Figure 2.

Figure 2: Age distribution of the cohort



The comparison of baseline demographic variables between the two groups is as shown in

Table 2. As seen, all the demographic variables were comparable between the two groups.

Table 2: Baseline demographic variables distribution between the two groups.

Parameter	Sevoflurane	Propofol	P value
Age in years (mean, SD)	59.46 (10.08)	59.34 (6.87)	0.95
Sex (male: female)	28:7	30:4	0.49
BMI	25.36 (4.01)	26.32 (3.68)	0.31
DM	24 (68.5%)	25 (73.5%)	0.65
HTN	19 (54.3%)	17 (50 %)	0.72
TEE grade (ascending aorta, I: II: III: IV)	2:29:4:0	8:24:1:1	0.63
Grade III-V	4 (11.4%)	2 (5.9%)	
TEE grade (arch)	0:27:7:1	5:19:7:3	0.53
Grade III-V	8 (22.8%)	10 (28.6%)	
TEE grade (descending aorta)	0:23:11:1	5:17:8:4	0.93
Grade III-V	12 (34.3%)	12 (35.3%)	

Operating Time

The mean (SD) CPB and cross clamp times are as provided in the table. As all other demographic variables, these parameters were also comparable between the sevoflurane and propofol groups.

Table 3: Comparison of CPB and cross clamp times between the two groups.

Parameter	Sevoflurane	Propofol	P value
CPB time (minutes)	136.2 (36.4)	127.4 (39.8)	0.36
Cross clamp time (minutes)	73.2 (22.1)	64.9 (24.0)	0.16

Cerebral oxygenation

The comparison of the cerebral oxygenation as measured by NIRS (left and right) at different time points is as shown in Table 4 (A and B) and Figure 3 (A and B). The mean NIRS values at intubation, CPB, cross clamp, moderate hypothermia, rewarming, after CPB and after sternal closure were comparable between the two groups as shown.

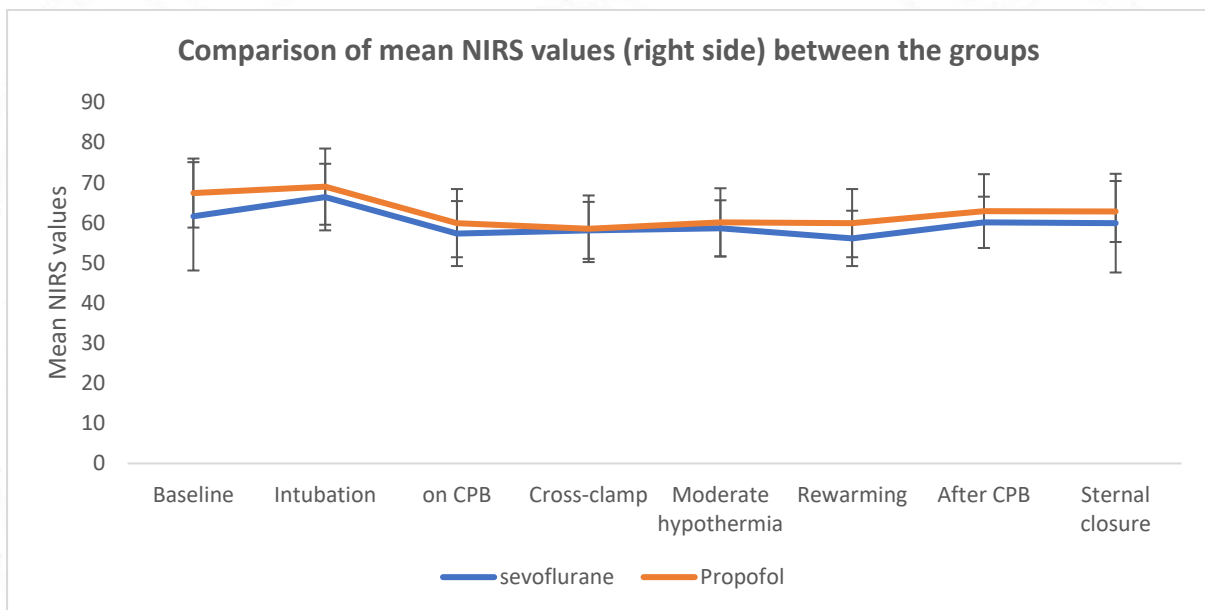
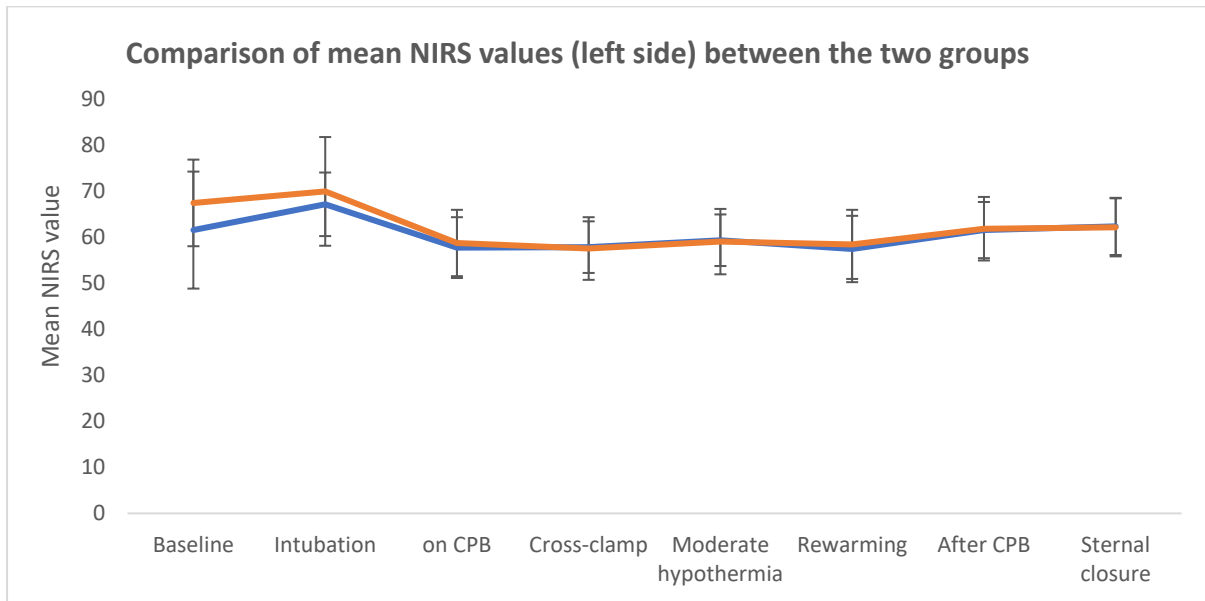
Table 4 (A): Comparison of NIRS values (mean, SD, left side) between the study groups.

Time	Sevoflurane	Propofol	P value
Baseline	61.5 (12.7)	67.4 (9.4)	0.03*
Intubation	67.1 (6.9)	69.9 (11.8)	0.24
On CPB	57.7 (6.6)	58.7 (7.2)	0.54
Cross clamp	57.8 (5.6)	57.5 (6.8)	0.81
Moderate hypothermia	59.3 (5.6)	59 (7.1)	0.85
Rewarming	57.4 (7.2)	58.4 (7.5)	0.56
After CPB	61.5 (6.1)	61.8 (6.9)	0.86
Sternal closure	62.3 (6.2)	62.1 (6.3)	0.87

Table 4(B): Comparison of NIRS (mean, SD, right side) between the study groups.

Time	Sevoflurane	Propofol	P value
Baseline	61.6 (13.5)	67.4 (8.6)	0.04*
Intubation	66.4 (8.3)	69 (9.5)	0.23
On CPB	57.3 (8.1)	59.9 (8.5)	0.20
Cross clamp	58.1 (7.1)	58.5 (8.3)	0.78
Moderate hypothermia	58.6 (7.0)	60.1 (8.5)	0.45
Rewarming	56.1 (6.9)	59.9 (8.5)	0.06
After CPB	60.1 (6.4)	62.9 (9.2)	0.26
Sternal closure	59.9 (12.3)	62.8 (7.6)	0.25

Figure 3 (A, B): comparison of mean NIRS values (left, right) between the two groups.



Arterial Blood Gas analysis

The ABG values at baseline, on CPB and post CPB are comparable between the two groups.

The variables analyzed included pH, pCO₂, pO₂, hemoglobin, potassium, sodium, calcium, and bicarbonate. These have been shown in Table 5 (A, B, C) below.

Table 5 A: Comparison of ABG between the two groups at baseline.

Baseline	Sevoflurane	Propofol	P value
PH	7.39 (0.05)	7.4 (0.03)	0.75
PCO ₂	38.03 (4.61)	37.42 (3.89)	0.56
PO ₂	121.15 (62.80)	130.87 (89.43)	0.60
Hemoglobin	12.97 (1.86)	13.81 (1.50)	0.053
Potassium	3.79 (0.42)	3.78 (0.75)	0.93
Sodium	137.25 (3.35)	136.63 (3.03)	0.45
Calcium	0.91 (0.35)	1.00 (0.29)	0.26
Bicarbonate	21.61 (8.03)	22.25 (4.87)	0.69

Table 5 B: Comparison of ABG values during CPB between the two groups.

	Sevoflurane	Propofol	P value
PH	7.41 (0.06)	7.39 (0.04)	0.25
PCO2	36.65 (5.36)	37.28 (4.43)	0.59
PO2	248.54 (103.76)	236.73 (65.73)	0.57
Hemoglobin	8.49 (1.35)	8.56 (1.18)	0.82
Potassium	4.38 (0.57)	4.37 (0.52)	0.93
Sodium	137.67 (3.95)	136.93 (3.65)	0.45
Calcium	1.01 (0.37)	1.09 (0.22)	0.24
Bicarbonate	22.21 (7.11)	22.91 (1.91)	0.18

Table 5 C: Comparison of ABG post CPB values between the groups.

	Sevoflurane	Propofol	P value
PH	7.37 (0.06)	7.35 (0.05)	0.13
PCO2	38.41 (5.92)	39.72 (4.62)	0.31
PO2	210.88 (85.76)	210.21 (93.39)	0.97
Hemoglobin	9.84 (1.43)	9.94 (1.24)	0.76
Potassium	3.74 (0.51)	3.86 (0.62)	0.39
Sodium	137.52 (2.86)	137.34 (3.24)	0.83
Calcium	0.87 (0.37)	0.99 (0.28)	0.17
Bicarbonate	20.31 (6.58)	22.26 (3.93)	0.14

Nadir values of NIRS, hemoglobin and PaO₂

The nadir values of NIRS (indicating depth of anesthesia), hemoglobin and PaO₂ were compared between the sevoflurane and propofol groups. The groups were comparable apart from the hemoglobin value which was marginally lower in the sevoflurane group compared to propofol (p value 0.047). These have been represented in Table 6 below.

Table 6: Comparison of mean nadir NIRS, Hb, and PaO₂ between the two groups.

	Sevoflurane	Propofol	P value
NIRS	52.7 (5.7)	54.1 (6.0)	0.36
Hb	7.6 (2.5)	8.5 (1.2)	0.047
PaO ₂	110.5 (30.8)	107.7 (34.2)	0.35

Glycemic control

The blood sugar values (mg/dL) at baseline, on CPB and post CPB are as represented in Table 7 below. The blood sugar values were comparable between the two groups.

Table 7: Comparison of mean blood sugar values (mg/dL) between the two groups.

	Sevoflurane	Propofol	P Value
Baseline	114.6 (25.5)	129.8 (39.1)	0.06
CPB	146.7 (34.4)	157.6 (39.5)	0.25
Post CPB	172.9 (37.6)	180.5 (37.9)	0.41

The mean time to wakefulness after surgery was comparable between sevoflurane (mean 3.6 hours, SD 2.2) and propofol (mean 3.6 hours, SD 1.4 hours), p value 0.9.

Post-operative delirium

Assessment for delirium was done on post-operative day 1 and day 2 by the CAM-ICU scale. Fifteen (21.7%) patients in the cohort developed delirium. The incidence of delirium was higher in the sevoflurane group compared to propofol as shown in Table 8 below.

Table 8: Comparison of the incidence of delirium on POD 1, POD 2 and total incidence between the two groups.

	Sevoflurane	Propofol	P value
POD 1	11/35 (31.4 %)	2/34 (5.8 %)	0.006*
POD 2	7/35 (20 %)	1/34 (2.9 %)	0.026*
Total incidence of delirium	12/35 (34.2 %)	3/34 (8.8%)	0.03*

Total 12 (34%) patients in Sevoflurane group developed delirium of which 5 patients had delirium on both the days. In propofol group only 3 (8.8%) patients developed delirium

The Odds ratio (OR) for developing delirium was significantly higher in the sevoflurane group compared to propofol as shown below.

Total incidence OR 1.72 (95% CI: 1.13-2.62), p 0.027*

Early post-operative cognitive dysfunction (POCD)

The mean (SD) values of MOCA scores at baseline and POD 7 are as shown in Table 9. The change in MOCA score was higher in the sevoflurane group and showed a trend towards statistical significance. Moreover, the incidence of early POCD (defined by a more than 2-point reduction in MOCA compared to baseline) was higher in sevoflurane (57.1%) compared to propofol group (32.3%). Overall, 31 (44.9%) patients had early POCD in the cohort.

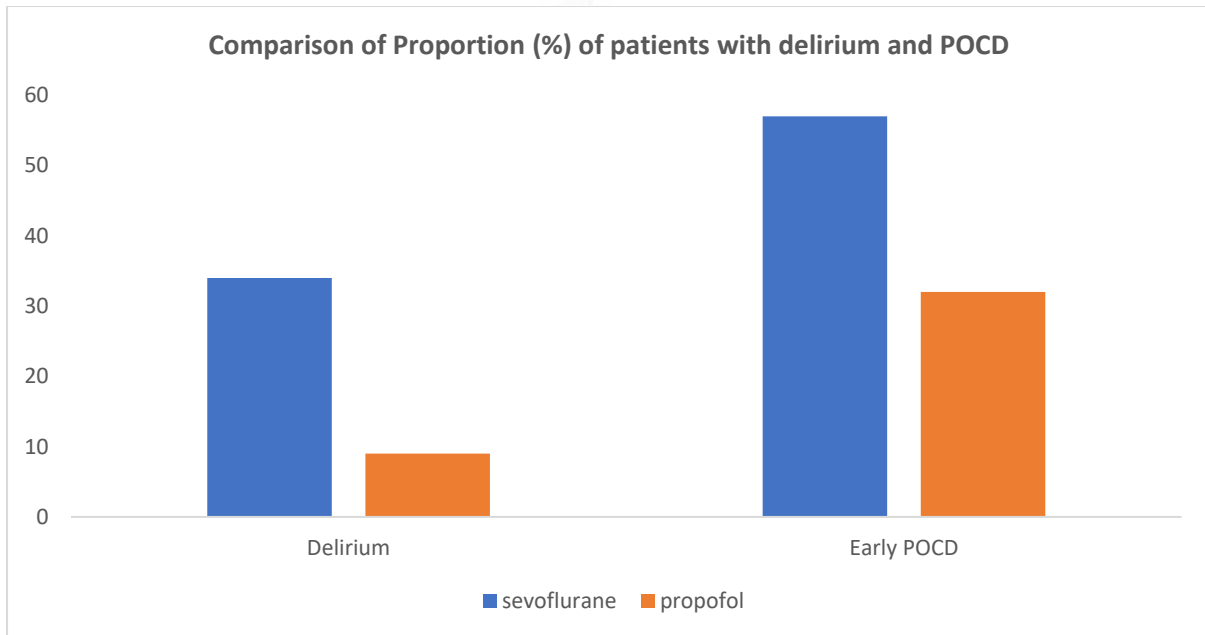
The comparison of delirium and POCD in the cohort has been provided in Figure 4.

Table 9: Comparison of MOCA scores at baseline, POD 7, change in MOCA score and proportion with early POCD between the two groups.

	Sevoflurane	Propofol	P value
Baseline MOCA	27.42 (1.01)	27.61 (1.21)	0.48
MOCA POD 7	24.77 (1.97)	25.64 (2.26)	0.10
Change in MOCA	2.65 (1.91)	1.97 (1.91)	0.068 (non-parametric test)
POCD (reduction in MOCA > 2 compared to baseline)	20/35 (57.1%)	11/34 (32.3%)	0.04*

OR for POCD in sevoflurane compared to propofol was 1.63 (95% CI: 1.01-2.62), p value 0.038*

Figure 4: Comparison of proportion (%) of patients with delirium and early POCD in the cohort (p values delirium 0.03* and early POCD 0.04*).



Factors associated with post-operative delirium

While comparing the demographic and intraoperative variables between patients who developed delirium with those who did not develop delirium, the patients who had delirium were more elderly. The rest of the variables such as BMI, CPB time, cross clamp time, baseline MOCA score, Katz atheroma grades, nadir values of NIRS, hemoglobin and oxygen saturation were comparable between the two groups. These are depicted in Tables 10 and 11.

Table 10: Comparison of baseline and intraoperative variables in those with and without delirium.

	Delirium	No delirium	P value
Age in years	64.44 (7.15)	57.82(8.51)	0.01*
BMI	26.47 (3.58)	25.66 (3.94)	0.48
CPB time min	136.61 (35.30)	130.50 (39.09)	0.61
Cross clamp time min	77.76 (24.36)	66.76 (22.72)	0.13
Time to wakefulness (hours)	3.56 (2.68)	3.62 (1.54)	0.93
MOCA baseline	27.25 (1.29)	27.10 (1.04)	0.26
Sugars on CPB	167.25 (38.40)	179.52 (37.34)	0.26
Katz grade III IV V			
Ascending aorta	1 /16	5/ 53	0.11
Arch	6/16	12/53	0.42

Descending aorta	5/16	20/53	0.57
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Table 11: Comparison of nadir values of NIRS, hemoglobin and pO2 in those with/ without delirium.

	Delirium	No delirium	P value
Nadir NIRS	52.7 (4.5)	53.6 (6.2)	0.58
Nadir pO2 (mm)	101.8 (35.3)	104.7 (31.7)	0.75
Nadir Hb (g/dl)	7.3 (2.3)	8.2 (1.9)	0.10

Sub-group analysis in the sevoflurane and propofol groups

We further performed a subgroup analysis to ascertain whether any of the above-mentioned intraoperative variables differed in the subgroups of sevoflurane and propofol with/ without delirium. All the variables were comparable between the groups. These have been shown in the Table 12.

Table 12: Comparison of intra-operative variables between the various subgroups.

	Sevoflurane Delirium	Sevoflurane No delirium	Propofol Delirium	Propofol No delirium	P value (ANOVA)
CPB time (min)	143.8 (35.3)	133.1 (37.2)	105 (17.6)	129.7 (40.9)	0.48
Cross clamp time (min)	81.7 (25.9)	69.8 (20.1)	59.3 (9.5)	65.5 (25.1)	0.28
Time to wakefulness (hr.)	3.7 (3.0)	3.6 (1.8)	3.3 (1.5)	3.6 (1.3)	0.98

TEE grade III- V	Sevoflurane Delirium	Sevoflurane No delirium	Propofol Delirium	Propofol Delirium	P value (ANOVA)
Ascending aorta	0/12	4/23	1/3	1/31	0.08
Arch	4/12	4/23	2/3	8/31	0.28

Descending aorta	2/12	10/23	2/3	10/31	0.27
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	Sevoflurane Delirium	Sevoflurane No delirium	Propofol Delirium	Propofol No delirium	P value (ANOVA)
Nadir NIRS	53.5 (4.7)	52.3 (6.3)	49.7 (3.5)	54.5 (6.1)	0.39
Nadir Hb	7.1 (2.5)	7.8 (2.6)	7.9 (1.5)	8.6 (1.1)	0.17
Nadir Po2	102.7 (40.6)	99.3 (25.2)	94.5 (11.7)	109.1 (35.4)	0.70
Inotropy score	6.2 (0.4)	6.2 (0.7)	5.7 (0.6)	6.1 (0.7)	0.67

Propofol delirium Vs Sevoflurane delirium the Nadir Hb was comparable ($p = 0.52$)

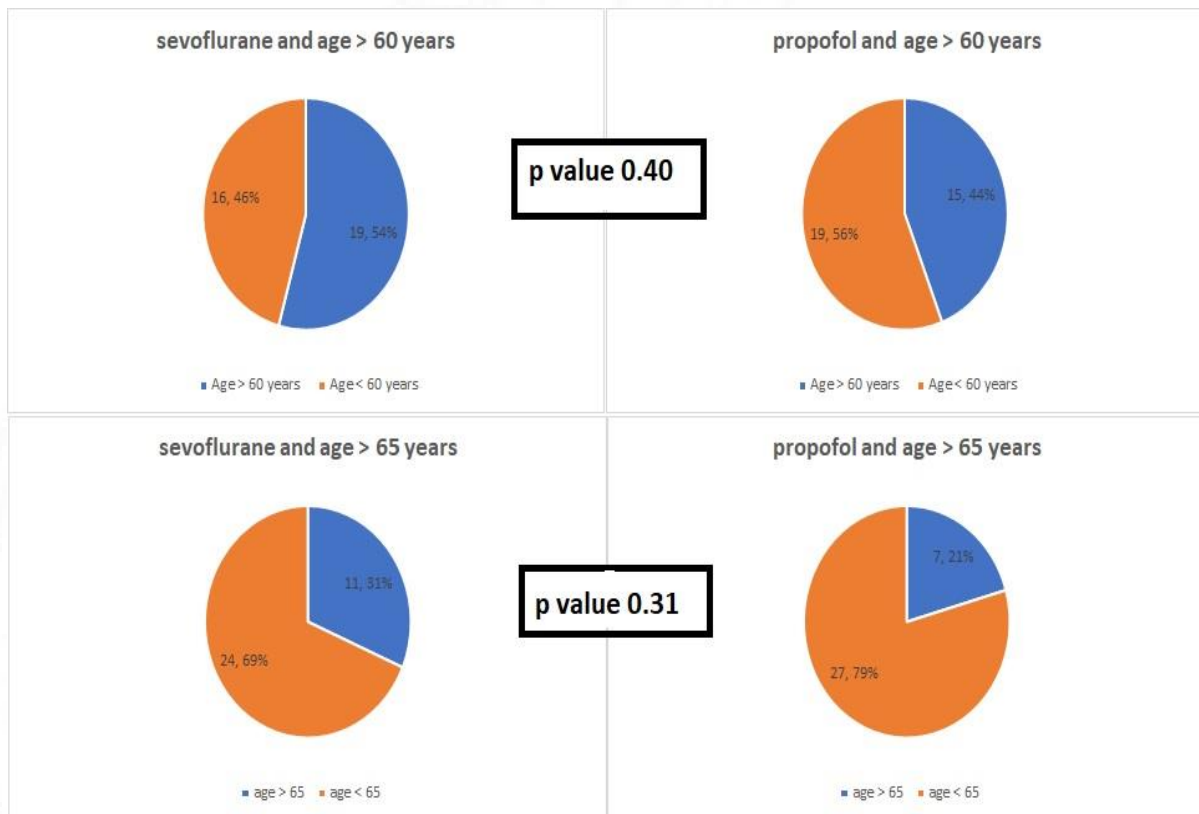
Propofol no delirium Vs Sevoflurane delirium Nadir Hb was significantly low in Sevoflurane ($p = 0.032$)

Age, sevoflurane-propofol and delirium

We performed a subgroup analysis to see the distribution of elderly patients between the sevoflurane and propofol subgroups. There was no significant difference in the distribution of

elderly patients (age > 60 years and age > 65 years) between the two groups respectively. This has been depicted in Figure 5.

Figure 5: Comparison of sevoflurane and propofol groups with respect to distribution of elderly patients (age > 60 years and age > 65 years).



Eight (42.1%) out of 19 elderly (age > 60 years) patients who received sevoflurane developed delirium whereas 2 (13.3%) out of 15 elderly (age > 60 years) who received propofol developed delirium. There was trend towards statistical significance with p value 0.067. In elderly patients, sevoflurane use was associated with higher risk of delirium compared to propofol.

In patients age more than 65 years, 7/ 11 (63.6%) patients who received sevoflurane developed delirium in contrast to propofol where only one of the 7 (14.2%) patients developed delirium. This difference was statistically significant, p value 0.03*.

Factors associated with early post-operative cognitive dysfunction (POCD)

While comparing the demographic and intraoperative variables between patients who developed early POCD with those who did not develop early POCD, the patients who had early POCD were more elderly. The rest of the variables such as BMI, CPB time, cross clamp time, baseline MOCA score, Katz atheroma grades, nadir values of NIRS, hemoglobin and oxygen saturation were comparable between the two groups. These are depicted in Table 13.

Table 13: Comparison of baseline and intraoperative variables in those with and without early POCD

	Early POCD	No POCD	P value
Age in years	62.93 (6.80)	56.54 (8.97)	0.002*
BMI	24.94 (3.85)	26.55 (3.75)	0.09
CPB time min	137.03 (44.55)	127.81 (32.64)	0.34
Cross clamp time min	72.11 (26.14)	66.72 (21.01)	0.37

Time to wakefulness (hours)	3.95 (2.08)	3.32 (1.60)	0.16
MOCA baseline	27.45 (1.12)	27.57 (1.10)	0.64
Sugars on CPB	154.10 (36.23)	150.41 (38.24)	0.68
Katz grade III IV V			
Ascending aorta	3/31	3/38	0.79
Arch	9/31	9/38	0.61
Descending aorta	12/31	12/38	0.54

	Early POCD	No POCD	P value
Nadir NIRS	52.29 (6.03)	54.32 (5.68)	0.55
Nadir pO2 (mm)	107.83 (38.95)	101.01 (26.22)	0.39
Nadir Hb (g/dl)	7.82 (1.78)	8.22 (2.22)	0.42

Table 14: Days of ICU stay between the subgroups

	Delirium	No delirium	P value
sevoflurane	2.83 (1.19)	2.13 (0.34)	0.012*
Propofol	2.33(0.57)	2.48 (0.51)	0.63

The duration of ICU stay between the two groups is as shown in Table 14. Longer ICU stay in the “no delirium” patients in the propofol group was due to development of atrial fibrillation .



DISCUSSION

Discussion

Cardiac surgery especially CABG is a commonly performed procedure worldwide. Though there have been significant declines in mortality, there remains an unmet need to reduce the post-operative complications and morbidity associated with these procedures. Delirium is a confusional state with alterations in consciousness, attention, cognition, and perception. Post-operative delirium in cardiac surgery results in longer hospitalisation, increased cost burden associated with higher morbidity. After CABG, post-operative delirium has been described in 26 to 52%¹ and nearly 35-60%.^{14,65} have cognitive dysfunction at time of discharge from hospital. Some of these changes can be described as a complication of surgical stress overlapping with declining cognitive reserve in ageing. However, identifying factors associated with post-operative delirium and cognitive dysfunction and reducing their incidence and improving post-operative outcomes remains a major goal in cardiac surgery.

Cardiopulmonary bypass is associated with activation of systemic inflammatory response, ischemia reperfusion injury, gut translocation of endotoxins and release of athero-emboli and micro embolism during cross clamping and cannulation. All these have been implicated in development of delirium and POCD post CPB. But studies like the ROOBY trial and meta-analysis comparing OPCAB with on pump CABG have not shown any increase in incidence of delirium or POCD with the use of CPB.^{28,66}

Meta-analysis by Greaves et al⁶⁷ on the cognitive outcomes after CABG concludes that delirium and cognitive dysfunction are major issues after CABG and requires specific attention. They also noted that incidence of delirium in various studies was heavily

influenced by the diagnostic test used and have emphasised on the use of a validated diagnostic instrument like CAM. We have used the well validated CAM-ICU score for the diagnosis of post-operative delirium in our study.

Recent advances in neuroprotection and neuromonitoring during cardiac surgery such as maintaining cerebral oxygenation using NIRS can potentially improve neurological outcomes after both cardiac and non-cardiac surgeries thus resulting in lesser morbidity. Studies have shown that maintaining NIRS above baseline throughout the procedure reduces the length of ICU stay^{68,69} and POCD⁷⁰. Though in our study the NIRS on CPB was found to be below baseline in both the groups, it was never allowed to drop below 20% of the baseline which is considered significant. The cause of NIRS drop was immediately sought and corrected as per NIRS algorithm⁶⁸ (maintain pump flows >2.4 l/min/m², MAP >60 mm Hg, Hct > 24 , PCO₂ between 35-45 mm hg, adequate depth of anaesthesia based on BIS, increasing FiO₂, adjusting position of neck to prevent kinking or pressure on blood vessels, checking position of cannula). NIRS was never allowed to drop below 20% of the baseline in any subjects for more than 40 seconds. Recent metanalysis by Zorilla et al⁷⁰ concluded that monitoring NIRS intraoperatively is associated with reduction of POCD and ICU stay. Hence, we maintained the NIRS above 20% of the baseline in both the groups to exclude a decline in cerebral oximetry as a cause of delirium and early POCD.

We have maintained the MAP on CPB >60 mm Hg since this is considered as the autoregulation limit in most individuals. We also maintained the upper limit of MAP on CPB < 80 mm Hg as studies have shown that higher MAP on CPB is associated with higher embolic load to brain and also increased risk of cerebral oedema.^{65,71}

We have only assessed early POCD at day 7 of surgery since POCD incidence is highest at day 7 after CABG in elderly and at 3 months was found to be independent of surgery or anaesthesia used.¹³

Intraoperative atheroma burden has been implicated in POCD after cardiac surgery at 1 week after surgery.⁷² Aortic plaque disruption releases micro emboli into circulation which can cause cognitive decline. In our study we have done a preoperative TEE examination to know the aortic atheroma burden and found that it was comparable in both the groups and we did not find any significant correlation between atheroma grading and development of POCD.

The implication of anaesthetic agents in delirium and cognitive dysfunction following cardiac surgery remains uncertain. Sevoflurane and propofol are two commonly used anaesthetic agents in cardiac surgery. There have been randomized trials and meta-analysis comparing the incidence of post-operative delirium and cognitive dysfunction using sevoflurane and propofol mainly in the context of non-cardiac surgery. There is relatively limited literature comparing the two agents in cardiac surgery. A recent study by Shin et al⁶⁰ has compared sevoflurane with propofol in the incidence of post-operative delirium after cardiac surgery. They concluded that overall incidence of delirium in both the groups were similar and that hyperactive delirium incidence was lesser in the sevoflurane group. However, it should be noted that the sevoflurane group received dexmedetomidine infusion with sevoflurane while the propofol group did not. Dexmedetomidine has been found to be protective against post-operative delirium. This could explain the comparable outcomes in both the groups.

A recent meta-analysis by Li et al⁷³ shows that dexmedetomidine use reduces the incidence of post-operative delirium after adult cardiac surgery. They also concluded that post-operative use of dexmedetomidine was the ideal time of use to prevent delirium. Thus in our study postoperative dexmedetomidine infusion was started on ICU in both the groups to minimise the risk of development of post-operative delirium.

Strengths of the study

The present study was a randomized, single blinded study comparing sevoflurane versus propofol in adult patients undergoing elective CABG under CPB. The main objective was to determine the incidence of post-operative delirium and early post-operative cognitive dysfunction in the cohort and analyse which of the two agents was associated with a higher risk of adverse post-operative cognitive outcomes.

In this randomized, single blinded study, we recruited 36 patients in each arm to receive either anaesthesia with sevoflurane or propofol during cardiac surgery and assessed their post-operative outcomes. The sample size was calculated based on a prior study by Ishii et al⁶¹, who demonstrated a lower incidence of postoperative delirium with propofol (6.9%) compared to sevoflurane (26.7%). The patients were randomised into the two groups using computer-generated random numbers placed in sequentially numbered opaque sealed envelopes. Surgical technique and anaesthesia were standardised for all cases as they were performed in a single hospital (a tertiary care centre in south India). Our primary aim was to compare incidence of postoperative delirium in cardiac surgery between the two anaesthetic agents used during CPB.

To avoid any confounders and to ensure a homogeneity of the study population, we carefully selected the study population to include patients who were undergoing elective CABG under

CPB. Since preoperative cognitive decline is an important factor associated with development of post-operative delirium and cognitive dysfunction⁷⁴ we excluded subjects with any cognitive decline from our study by doing a baseline MOCA scoring. Also subjects with any known risk factor for delirium and POCD like psychiatric illness, use of psychotropic drugs and neurologic dysfunction were excluded. The baseline demographic variables such as age, sex, body mass index, co-morbidities, and baseline MOCA scores were comparable between the study groups. All patients underwent standard monitoring with NIRS and bispectral index (BIS) to ensure optimal cerebral oxygenation and adequate depth of anaesthesia.

All the intra-operative variables such as Katz scores for atheroma grading, CPB time, cross clamp time, time to wakefulness, NIRS scores and ABG parameters during different phases of surgery, nadir NIRS score, nadir haemoglobin, oxygenation and ionotropic scores were comparable between the two groups.

We assessed both post-operative delirium (on POCD 1 and 2) and early post-operative cognitive dysfunction (change in MOCA at day 7 compared to baseline) with standardized assessment methods which have already been validated and have undergone cross cultural adaptation. All the post-operative delirium assessments and MOCA scorings were done by a single investigator who was well versed with the use of MOCA scoring and CAM-ICU scoring systems. Hence, we were able to objectively define outcomes with minimal interference from the confounders and risk of bias. Moreover, this is one of the first reported studies from India which potentially addresses this important concern regarding anaesthesia use and post-operative delirium/ cognitive dysfunction following CABG.

Summary of our findings

The mean age of our study population was 59.4 years (SD 8.6 years), and thirty-four patients (49.3%) were older than 60 years. All the baseline demographic and intra-operative variables were comparable between the two groups as already mentioned before. Fifteen patients (21.7%) developed postoperative delirium and 31 (44.9%) had early post-operative cognitive dysfunction. The use of sevoflurane was associated with a higher risk of developing both delirium (OR 1.72, p 0.027*) and early postoperative cognitive dysfunction (OR 1.63, p 0.038*). Both delirium and early postoperative cognitive dysfunction were seen more in elderly. In elderly patients, sevoflurane use was associated with higher risk of delirium compared to propofol. This difference was especially prominent in patients > 65 years. Delirium in the sevoflurane group was associated with a short but statistically significant increase in duration of ICU stay.

Rationale for study observations

The incidence of postoperative delirium and cognitive impairment is similar to other studies reported in literature. The higher incidence of delirium and POCD in the sevoflurane group can be attributed to multiple factors. It has been reported in previous studies that the proinflammatory markers following surgical stress are higher with inhalational anesthetics and that propofol might actually reduce some of these cytokines causing neuroinflammation⁷⁵. Neurotoxicity with amyloid-beta deposition has been described with inhalational anesthesia.³⁴ This deposition can cause an adverse cognitive profile. Inhalational anaesthetic agents have also been shown to promote neuronal apoptosis leading to reduced cognition in the postoperative period.⁷⁶ Sevoflurane use has been postulated to promote progression of amnesic mild cognitive impairment.⁷⁷ Propofol has been postulated to reduce sevoflurane

neurotoxicity. There is a possible hypothesis that better pain relief with propofol compared to sevoflurane might translate potentially into lesser incidence of delirium and less neurocognitive impairment.^{78,79} All these changes are more likely in elderly patients with decreased cognitive reserve.

It has also shown addition of methylprednisolone to inhalational anaesthetic to reduce POCD by attenuating the inflammatory responses. The main inflammatory cytokines implicated in pathogenesis include TNF-alpha and IL-6. These markers and S100beta (a marker for acute brain injury) have been shown to be upregulated following sevoflurane anesthesia.⁶³

Conversely, propofol has demonstrated to inhibit the activation and release of cytokines by the astrocytes.⁸⁰ Higher levels of IL-10, which is an anti-inflammatory cytokine (also known as human cytokine synthesis inhibitory factor) besides lower IL-6 have been found with propofol compared to sevoflurane.⁸¹

It is worth mentioning that there are observations from preclinical studies that use of inhalational anesthetic is associated with better preconditioning by reducing the ischemia-reperfusion injury in several organs.^{38,39} But these concepts have seldom been proven in the context of clinical trials. Metanalysis comparing inhalational agents with propofol have shown results favoring neither drug even from a cardiac perspective. The concept hence remains a paradox.

Comparison with previous studies

A recent meta-analysis analysing outcomes after CABG in its subgroup analysis reported no significant difference in the incidence of PD or postoperative cognitive impairment between inhalation anaesthetics and propofol after coronary artery bypass graft surgery.⁸² There were

8 trials assessing POCD and 3 trials assessing delirium in this meta-analysis. There was no statistically significant difference between the volatile anaesthetics and TIVA groups in the incidence of delirium (RR = 0.96, 95% CI: 0.71–1.29, $p = 0.78$, without heterogeneity).

There was no statistically significant difference between the volatile anaesthetics and TIVA groups in the incidence of postoperative cognitive impairment (RR = 1.20, 95% CI: 0.74–1.94, $p = 0.46$), with moderate heterogeneity ($I^2 = 59\%$).

In non-cardiac surgery, two separate meta-analysis have indicated conflicting reports. Miller et al. had concluded that there was no difference based on the anaesthetic agent.⁵⁵ Pang et al.⁶ reported that there was moderate-level evidence that propofol was associated with lesser postoperative cognitive dysfunction and low-level evidence that there was less severe systemic inflammatory response after propofol compared to inhalational anaesthetics. S-100 B protein (which is a biomarker of acute brain injury) was lower after propofol. The difference in POCD was different between the two groups on POD 2-6. There was some heterogeneity in view of the different assessment methods used. The levels of TNF alpha and IL-6 were reduced in the propofol group on POD 1. It is possible that the higher levels of pro-inflammatory cytokines could have resulted in a higher neuroinflammation and cognitive dysfunction in the inhalational anaesthesia group as mentioned before.

In this context, two studies performed in patients undergoing cardiac surgery need mention. Schoen et al. had analysed cognitive functions by the abbreviated mental score (AMT) test starting 2 days after surgery⁸³. They reported that the incidence of POCD was higher in patients who had cerebral desaturations and in those receiving propofol. It needs to be highlighted that majority of the patients who actually had desaturation were older and had a lower baseline cognitive assessment score, showing a lesser cognitive reserve. The

assessments at day 2 could be completed in only 53%. There were a higher number of patients requiring complex procedures in the propofol group. Moreover, the AMT is inferior to CAM for delirium assessments and there was no clinical significance in terms of increased ICU stay or hospitalisation between the groups. The study inferred that sevoflurane use was probably associated with lesser cognitive impairment probably even related to the “ischemic preconditioning hypothesis”. However, in view of the limitations mentioned above, the results need to be interpreted with extreme caution.

Royse et al. reported a higher incidence of early POCD (at the time of discharge and in propofol (67.5%) compared to desflurane (49.4%) in patients undergoing CABG⁸⁴. The baseline parameters were comparable between the two groups. There was no difference in the incidence of delirium and cognitive impairment at 3 months. Some confounders which could have limited interpretation of this study include the facts that there were more wound site infections in the propofol group, role of confounding drugs such as midazolam or fentanyl and the stringent neuropsychological battery of tests used. The length of the hospital stays also did not differ between the two groups.

Kitamura et al⁸⁵ in their study have shown that use of propofol was associated with lower blood glucose levels than sevoflurane in non-diabetic patients undergoing various surgeries. Hence we wanted to see if this was true in cardiac surgery as well where stress response is high and glucose levels can rise significantly. However we found no statistical difference in the glycaemic control in the two groups. This was similar to the findings of Kim et al⁸⁶ who found no significant difference in the incidence of hyperglycaemia among the two groups in patient undergoing lung surgeries

Limitations of the study

Some limitations of the study include (a) the relatively small sample size, (b) the fact that all the cases were done in a single centre with a standardized protocol for management and monitoring, which might limit the generalisation of the results, (c) inflammatory cytokines and biomarkers were not assessed to correlate with delirium and cognitive dysfunction as it was outside the scope of the study, (d) the lack of a longer follow-up at 6 weeks, 3 months and one year to assess the consequences (if any) and clinical significance of delirium and POCD in our cohort, (e) we did not limit our study cohort to the elderly as we felt that age could be a major confounder limiting assessment and differentiation between the study groups

Future Prospects

A large multi-centre randomized control trial with a homogenous population will help in providing more evidence to differentiate the effect of propofol and sevoflurane regarding post-operative delirium and cognitive outcomes. There might be a role for addition of dexmedetomidine which may help in reducing POCD as part of standard care in both arms.



CONCLUSION

CONCLUSIONS

1. Propofol based TIVA was associated with lesser incidence of delirium and cognitive dysfunction compared to sevoflurane in our cohort of adult patients undergoing elective CABG under CPB.
2. Both delirium and early post-operative cognitive dysfunction were seen more in elderly. In elderly patients, sevoflurane use was associated with higher risk of delirium compared to propofol. This difference was especially prominent in patients > 65 years.
3. Further large scale, multi-center, randomized trials with longer follow-up duration are needed to substantiate and in addition also analyze the long-term clinical relevance of this observation.
4. Future studies can also include inflammatory and oxidative markers to further elucidate the association and addition of novel agents such as dexmedetomidine which may potentially have a role in reducing post-operative delirium in the real-world setting.



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APPENDIX

APPENDIX -A

Proforma

Age: Sex: Group:

Ht: Wt: BMI: Comorbidities:

TEE (Atheroma) Asc Ao: Y/N Katz gr:

 Arch : Y/N Katz gr:

 Desc Ao: Y/N Katz gr:

NIRS: Baseline :

After intubation :

 On CPB :

After cross clamp :

At moderate hypothermia(30⁰c):

 Rewarming :

 After CPB :

 After sternal closure :

Sugars : A(baseline) : B(CPB) : C(Post CPB):

ABG: A

 B

 C

Time to full wakefulness: Days in ICU:

CAM-ICU score(POD 1):

 (POD 2):

MOCA score Baseline: (POD 7):

CPB duration

X clamp duration

APPENDIX D : CAM-ICU

CAM ICU Features and Descriptions						
1. Acute Onset or Fluctuating Course	Absent	Present				
<p>A. Is there evidence of an acute change in mental status from baseline? OR B. Did the abnormal behavior fluctuate during the past 24 hours (e.g., tend to come and go, or increase and decrease in severity as evidenced by fluctuation of the VAMASS, GCS, or previous delirium assessment)?</p>						
2. Inattention	Absent	Present				
<p>Did the patient have difficulty focusing attention as evidenced by scores less than 8 on either the auditory or the visual component of the Attention Screening Examination (ASE)?</p> <p>• Use the 5 + 5 pictures, or recognize a letter intermixed in a sequence of 10 letters</p>						
3. Disorganized Thinking	Absent	Present				
<p>Does the patient have disorganized or incoherent thinking as evidenced by incorrect answers to 2 or more of the following 4 questions and/or demonstrate an inability to follow commands?</p> <p>Questions (Alternate Set A and Set B):</p> <table style="width: 100%; border: none;"> <tr> <td style="text-align: center; width: 50%;">Set A</td> <td style="text-align: center; width: 50%;">Set B</td> </tr> <tr> <td style="vertical-align: top;"> <ol style="list-style-type: none"> 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? </td> <td style="vertical-align: top;"> <ol style="list-style-type: none"> 1. Will a leaf float on water? 2. Are there elephants in the sea? 3. Do 2 pounds weigh more than 1 pound? 4. Can you use a hammer to cut wood? </td> </tr> </table> <p>Other:</p> <ol style="list-style-type: none"> 1. Are you having any unclear thinking? 2. Hold up this many fingers (examiner holds up own fingers in front of patient). 3. Now do the same with the other hand (examiner demonstrates by displaying a different number of fingers). 			Set A	Set B	<ol style="list-style-type: none"> 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? 	<ol style="list-style-type: none"> 1. Will a leaf float on water? 2. Are there elephants in the sea? 3. Do 2 pounds weigh more than 1 pound? 4. Can you use a hammer to cut wood?
Set A	Set B					
<ol style="list-style-type: none"> 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does 1 pound weigh more than 2 pounds? 4. Can you use a hammer to pound a nail? 	<ol style="list-style-type: none"> 1. Will a leaf float on water? 2. Are there elephants in the sea? 3. Do 2 pounds weigh more than 1 pound? 4. Can you use a hammer to cut wood? 					
4. Altered Level of Consciousness	Absent	Present				
<p>Is the patient's level of consciousness anything other than alert (e.g., vigilant, lethargic, or stuporous), or is VAMASS < or >3 (and not decreased due to sedation)?</p> <p>Alert: Looks around spontaneously, fully aware of environment, interacts appropriately.</p> <p>Vigilant: Hyperalert.</p> <p>Lethargic: Drowsy but easily aroused. Unaware of some elements in the environment, or no appropriate spontaneous interaction with interviewer. Becomes fully aware and appropriate with minimal noxious stimulation.</p> <p>Stupor: Becomes incompletely aware with strong noxious stimulation. Can be aroused only by vigorous and repeated stimuli. As soon as stimulus removed, subject lapses back into unresponsive state.</p>						
Overall CAM ICU Score: If 1 + 2, and either 3 or 4 is present, patient has delirium.	Yes	No				

APPENDIX E: IEC CLEARANCE



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम - 695 011, केरल, भारत
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
TRIVANDRUM - 695 011, KERALA, INDIA
(एक राष्ट्रीय महत्व का संस्थान, विज्ञान एवं प्रौद्योगिकी विभाग, भारत सरकार)
(An Institution of National Importance, Department of Science and Technology, Government of India)
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Institutional Ethics Committee (IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1623/DECEMBER-2020

19.12.2020

Dr.Varsha AV
Senior Resident ,Cardiothoracic and Vascular Anaesthesia
Department of Anaesthesiology,
SCTIMST, Thiruvananthapuram

Dear Dr.Varsha AV,

Thank you for submitting documents related to your proposal titled "COMPARISON OF TOTAL INTRAVENOUS ANAESTHESIA VS INHALATIONAL MAINTENANCE OF ANAESTHESIA FOR EARLY POSTOPERATIVE DELIRIUM IN ADULT CARDIAC SURGERY: PROSPECTIVE RANDOMIZED DOUBLE BLINDED STUDY(IEC/1623)" to the IEC for review.

The following documents were reviewed:

1. Checklist
2. Covering letter addressed to the Chairman, IEC, SCTIMST dated 18.11.2020
3. Covering letter addressed to the Chairman, IEC, SCTIMST dated 18.11.2020 forwarded by HOD
4. IEC Application Form
5. TAC Approval Letter
6. Full proposal
7. Proforma
8. Patient Information Sheet in English
9. Informed Consent Form in English
10. Patient Information Sheet in Malayalam (Full mistake)
11. Informed Consent Form in Malayalam (Full mistake)
12. CV of Dr.Varsha AV with TCMC registration number
13. CV of Dr. Unnikrishnan KP with TCMC registration number
14. CV of Dr.Suneel PR with TCMC registration number
15. CV of Dr. Saravana Babu with TNMC registration number

The following members of the Students Sub-Committee of the Institutional Ethics Committee participated in the discussions held on Dec 9, 2020 at the offices and residences of the members

SL No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Hari Krishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
5.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
6.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,



Mala Ramanathan
Member Secretary, IEC

APPENDIX F : PLAGIARISM CHECK



Document Information

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SA	Tamil Nadu Dr. M.G.R. Medical University / DEXEMEDETOMIDINE VERSUS KETOFOL EFFECTS ON THE INCIDENCE OF EMERGENCE AGITATION ASSOCIATED WITH SEVOFLURANE BASED ANAESTHESIA IN CHILDREN UNDERGOING ADENOTONSILLECTOMY.pdf Document DEXEMEDETOMIDINE VERSUS KETOFOL EFFECTS ON THE INCIDENCE OF EMERGENCE AGITATION ASSOCIATED WITH SEVOFLURANE BASED ANAESTHESIA IN CHILDREN UNDERGOING ADENOTONSILLECTOMY.pdf (D42463914) Submitted by: joen.grasim@gmail.com Receiver: joen.grasim.mgrmu@analysis.arkund.com	2
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