

The Incidence of Cerebral Air Embolization with Two Modalities of Anesthesia in Pediatric Open Cardiac Surgery using Cardiopulmonary Bypass

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Abstract

Background: Neurological complications after pediatric open cardiac surgery represents a great challenge to all anesthetists. Cognitive domains may be affected with or without behavioral change. Cerebral air embolization and hypoperfusion are considered as fundamental causes. Transcranial Doppler can determine any air emboli entering brain circulation intra-operatively. Together with cerebral oximetry, they can detect any harmful embolic events during open cardiac surgery. New models of neuroprotective strategies were implanted to ameliorate this problem including different anesthetic medications like propofol and sevoflurane.

Methods: 120 patients who were planned for elective cardiac surgery were recruited in this study. Anesthesia was maintained with Propofol infusion at a rate of 150 µg/Kg/min or sevoflurane 1 MAC. Cerebral oximetry and transcranial Doppler sonography were used to monitor cerebral blood flow, air embolization and oxygenation with evaluation of their neurocognitive function using The Mini-Mental State Examination (MMSE).

Results: Embolic events were higher in sevoflurane group when compared to propofol group at insertion and removal of aortic cannula as well as on release of aortic cross clamp. Mean arterial pressure and mean velocity of middle cerebral blood flow were higher in sevoflurane group when compared with propofol group. Also velocity mean were lower in comparison to basal values in propofol group. MMSE score comparison between both groups were of no significant difference.

Conclusion: In comparison to sevoflurane, propofol decrease the incidence of cerebral air embolic events, mean cerebral blood flow velocity and MAP more than sevoflurane. Meanwhile, it has equivalent effect to sevoflurane regarding regional cerebral oxygen saturation and neurocognitive outcome.

Keywords: Neurological complications; Pediatric; Open cardiac surgery; Cognitive domains; hypoperfusion; Embolization; Transcranial doppler; Cerebral oximetry; Neuroprotective strategies; Pharmacological neuroprotective

Introduction

Neurological complications after surgery for correction of congenital cardiac anomalies represents a great challenge to all anesthetists. These neurological deficits are mostly subclinical with optimistic long term outcome, however cognitive impairments may continue to affect the neurological development and daily life [1,2]. Cognitive domains including attention, memory, learning, visual, motor skills, and executive function may be affected alone or accompanied by behavioral change [3]. There was a considerable interest in understanding the underlying mechanisms of neurological insult during open cardiac surgery. Three principle factors were demonstrated; cerebral hypoperfusion, cerebral arterial embolization, and systemic inflammatory response following CPB [4]. All these mechanisms were rooted mainly to air embolization and hypoperfusion. Air emboli presence in the cerebral circulation intra-operatively can reduce cerebral perfusion and obstruct blood flow by

either direct mechanical effect or by increasing platelets aggregation and thrombus formation. Also microemboli produce endothelial irritation and inflammation by stimulating the leucocytic activity and complement system cascade or by ischemic reperfusion injury [5-8].

In addition, circulating gaseous bubbles may induce functional endothelial injury with transient, increased permeability to macro and micro molecules. Moreover, a rise in brain water uptake, glucose utilization and protein extravasation are also associated with gaseous emboli [9]. Experimental cerebral air embolism is found to have a two-step effect on the brain. Shortly after air entry, there is multifocal brain lesion with widening of the extracellular space, later shrinkage and necrosis of neurons and neuronal sheath [10]. These microemboli can originate from bubble oxygenators, venous reservoirs, air in the CPB venous line, inadequate surgical deairing in open chamber procedures, introduction by perfusionist during drug administration and collection of blood samples, and entrainment of air into the blood in the cardiotomy suction and vacuum assisted drainage [11]. In addition, the process of cooling and reheating alter the solubility of the dissolved gases and facilitate formation of micro bubbles inside somatic blood vessels [12,13].

Currently, advanced monitors represent a fundamental tools for early recognition and implantation of preventive measures against embolic events. Transcranial Doppler (TCD) ultrasound monitor is highly sensitive to micro air emboli. It has the ability to discover thousands of air bubbles induced embolic signals in cerebral vasculature [14]. Although detecting these tiny bubbles in Cardiopulmonary Bypass (CPB) lines is easy nowadays, no previous studies have investigated the possibility of cerebral air embolization during open cardiac surgery and the implications of anesthetic drug on their incidence [15]. Together with cerebral oximetry, TCD can detect any harmful injurious agents including real-time detection and quantification of microemboli passing through the cerebral circulation in pediatric patients undergoing open cardiac surgery using CPB [11].

In order to improve the neurological outcome and specifically reduce embolic events, new models of neuro-protective strategies were implanted. These include better design of venous reservoirs, increased uptake of CPB arterial line filters, increased surgeon's awareness about air embolism impact, cell saver processing of cardiomy blood, meticulous perfusionist interventions, cooling, retrograde cerebral perfusion and adequate surgical deairing of all cardiac chambers [11]. Also, pharmacological neuroprotective strategies were recruited including, hyperbaric oxygen, barbiturate coma, lidocaine, oxygen and inotropic support and some anesthetic agents as well [16,17].

One of the common anesthetic drug used in neuroprotective method is propofol which causes inhibition of glutamate release, reduction in cerebral metabolic rate oxygen consumption with cerebral vasoconstriction [18,19]. Another important neuroprotective drug is sevoflurane that maintain the cerebral blood flow with dose dependent reduction in cerebral metabolic rate [20,21]. With the affordability of many methods to decrease cerebral gaseous embolization, it is difficult to assess whether the use of specific anesthetic agent can attenuate the embolic events. In this study, we hypothesises that propofol is more effective than sevoflurane in preventing the incidence of cerebral air embolism during CPB in pediatric patients undergoing open cardiac surgery for congenital heart diseases with better neurocognitive functions outcomes.

The principle aim of this study was to assess the effect of two different anesthetic medications (propofol and sevoflurane) on decreasing the number and amount of air emboli entering the Middle Cerebral circulation during open cardiac surgery using CPB. Additional outcome is to evaluate the effect of using those two different anesthetic medications on neurocognitive outcome through their embolic preventive and brain protective effects. In order to approach our aim, detected embolic events, mean cerebral blood flow velocity, MAP, cerebral oxygen saturation and neurocognitive assessment were investigated in both studied groups using mean arterial pressure transducer, transcranial doppler ultrasound device, cerebral oximetry and the Mini-Mental State Examination for children test.

Patients and Methods

This double-blind, randomized, comparative study was conducted on 120 patients of either sex aged 4-7 years who were subjected to elective correction of simple congenital heart diseases using cardiopulmonary bypass after obtaining an informed written consent from their parents/guardians. Patient with neurological, hepatic or renal diseases were excluded from the study.

Preoperative clinical examination and laboratory tests were full field according to our unit protocol. On arrival to operative theatre, patients

were randomly assigned (using closed envelope method) into two groups: propofol group and sevoflurane group. Standard monitoring (ECG, SpO₂ and NIBP) were connected to all patients before induction of anesthesia. Supplemental oxygen was provided via a face mask (using Datex monitor, Helsinki, Finland AS). One peripheral intravenous indwelling cannula were inserted in non-dominant hand after using EMLA cream to numb the insertion place.

Anesthesia was induced using I.V. fentanyl 5 µg/Kg, propofol 2-2.5 mg/Kg (in propofol group) or sevoflurane 3-4 MAC (in sevoflurane group). With loss of consciousness, patients were mechanically ventilated by positive pressure ventilation via face mask at a rate of 18-25 breathes per minute with 100% O₂ and 1 mg/kg rocuronium I.V. was given for ETT insertion. A triple lumen central line was inserted under complete aseptic condition in right internal jugular vein. An arterial line was inserted in right hand to monitor MAP at certain intervals, and facilitate blood sampling.

Nasopharyngeal temperature probe, cerebral oximetry, entropy probe as well as transcranial Doppler transducer were attached to the patient head for adequate monitoring. End-tidal CO₂ was monitored by side-stream capnograph. Anesthesia was maintained with Propofol infusion at a rate of 150 µg/Kg/min (in propofol group) [22], or sevoflurane 1 MAC (in sevoflurane group) and fentanyl 1 µg/Kg/min, to maintain state and response entropy reading between 40-45 and blood pressure within 75% of its basal value with additional doses of rocuronium (0.5 mg/Kg) to maintain muscle relaxation. A pressure controlled mode was used to ventilate all patients aiming at tidal volume 6-8 ml/kg and end tidal CO₂ between 30-35 mmHg.

Standard median sternotomy was used for heart approach. Ascending aorta, SVC and IVC were cannulated for cardiopulmonary bypass using a membrane oxygenator and a roller, non-pulsatile pump flow with average rate around 1.6-2.4 L/m²/min. During CPB, patients were ventilated with a minute volume of 0.5 liter at a frequency of 5 breaths/minute with a positive end-expiratory pressure of 5 cm H₂O. Before removal of the cross clamp, the heart was passively filled with blood with gentle massaging of left side and vented continuously. After releasing of the aortic ventilation of both lung were resumed. The preload was gradually increased by reducing the venous return to CPB, and transoesophageal echo was used to monitor and confirm the de-airing process. After completion of weaning from CPB, the left ventricle vent was stopped and clamped in situ [23].

Cerebral oximetry was used to monitor the regional tissue oxygenation together with transcranial doppler (TCD) sonography to monitor the velocities of blood flow in middle cerebral artery (CBFV), and incidence of air embolization through trans temporal window, (2.0/2.5 MHz TCD device, Toshiba Xeario model, 3MHz frequency). Although cerebral blood flow velocity is not a direct measurement of CBF, but changes in CBFV is closely correlate with the cerebral blood flow changes because the middle cerebral artery diameter is usually constant [24]. Mean velocity of flow was measured before induction of general anesthesia (basal), after insertion of aortic cannula, 15 minutes after establishment of CPB, on removal of cross clamp, and removal of aortic cannula. Emboli detection was done at different event markers; after insertion of aortic cannula, 15 minutes after establishment of CPB, after removal of cross clamp, and removal of aortic cannula. Event-related micro-emboli signals (MES) were defined as the micro emboli signals that were spotted within 180 second following an event marker. Another experienced radiographer had re-evaluated all stored Doppler signal events in a different session [22,23,25].

Micro-emboli signals were diagnosed by their standard visual characteristic appearance. Tiny emboli appear as an enhanced scattering and reflection of ultrasound waves from the embolus with short duration of high intensity signal within the Doppler flow spectrum in comparison to the surrounding red blood cells [26]. Also, small air bubbles have a definitive erratic high-pitched swishing roar or washing machine sound due to the turbulent resonance of normal blood flow passing through the blood vessels. If clusters of MES was detected, their number was estimated mainly on the roots of their visual appearance. The overall number of MES during the whole surgical procedure was further determined [27].

A researcher with experience in administration of neuropsychological tests were recruited for neuro-cognitive function assessment in this study using The Mini-Mental State Examination (MMSE). The Mini-Mental State Examination (MMSE) was designed for assessing the severity of impairments, and identifying changes in cognitive dysfunctions in a wide age range (3-14 years). Moreover, comprehension of instructions was independent of socioeconomic status and educational level. In the present study an adapted version of the MMSE, in a preschool- and school-aged sample. The final version was decided consensually, comprising 13 items covering five cognitive abilities (orientation, attention and working memory, episodic memory, language and constructional praxis) with a maximum score of 37 [28,29]. To familiarize the children with the test, we gave an explanation trial and perform a basal assessment for all participants. Postoperative cognitive function assessments were conducted in the ward or at anesthesia clinic after one week and three months after surgery.

Sample Size

Sample size of this study was calculated using PS software for Windows version 10 according to differences in number of microemboli detected in previous study. It revealed 54 patients in each arm to obtain power of about 80%. We increased the number of patients up to 60 patients in each arm to compensate 20% possible dropouts [30].

Statistical Analysis

Statistical analysis was done using statistical package for social scientists (SPSS) program version 17, USA, Chicago. The mean and standard deviation (SD) or median and interquartile range (IQR) were reported as appropriate for continuous data after checking data for normality using the Shapiro–Wilk test. Independent sample t test or Mann–Whitney U test were used to compare perioperative differences between groups. Chi–square test were used for qualitative data. P<0.05 was considered significant.

Results

All patients have completed the study successfully with no dropouts. No considerable differences were observed between two groups as regard demographic data and type of surgery (Table 1).

	Propofol Group (n=60)	Sevoflurane Group (n=60)	P value
Age (months)	63.42 ± 11.05	62.50 ± 10.55	0.89

Sex Male	70% (42)	60% (36)	0.22
Female	30% (18)	40% (24)	
Weight (kilogram)	25.06 ± 3.27	25.56 ± 2.57	0.081
ASD	50% (30)	45% (27)	0.36
VSD	50% (30)	55% (33)	

Table 1: Demographic data of the studied groups: Data are presented in number & % or mean ± SD.

Both cross clamp time and CPB time were almost the same in both groups (table 2).

	Propofol Group (n=60)	Sevoflurane Group (n=60)	P Value
Cross Clamp Time (min)	27.59 ± 5.89	28.65 ± 6.01	0.07
CPB Time (min)	321.89 ± 4.38	33.05 ± 5.47	0.081

Table 2: Aortic cross clamp time (min) and CPB time (min) in the studied groups, Data are in mean ± SD.

Mean arterial pressure showed statistically higher values in sevoflurane group when compared with propofol group after induction and at aortic cannula insertion. Also mean arterial pressure was statistically lower in propofol group when compared to basal value after induction, 15 minutes after establishment of CPB and after removal of cross clamp (Figure 1).

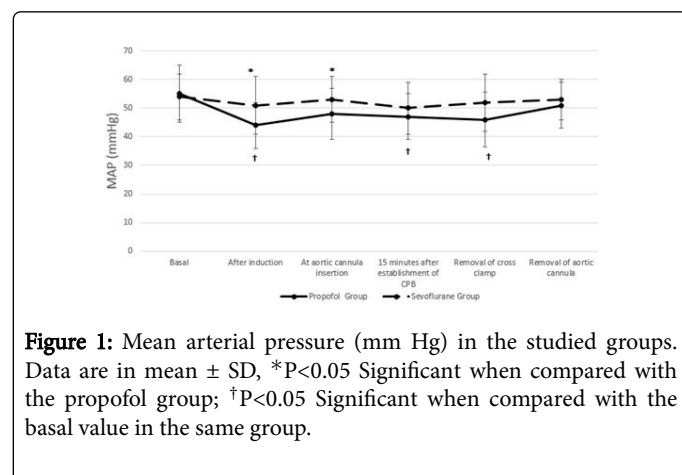


Figure 1: Mean arterial pressure (mm Hg) in the studied groups. Data are in mean ± SD, *P<0.05 Significant when compared with the propofol group; †P<0.05 Significant when compared with the basal value in the same group.

Velocity mean was significantly higher at aortic cannula insertion, 15 minutes after establishment of CPB and on removal of crossclamp in sevoflurane group when compared with propofol group. Also In propofol group, velocity mean were lower in comparison to basal values after induction, at aortic cannula insertion, 15 minutes after establishment of CPB and on removal of cross clamp (Figure 2).

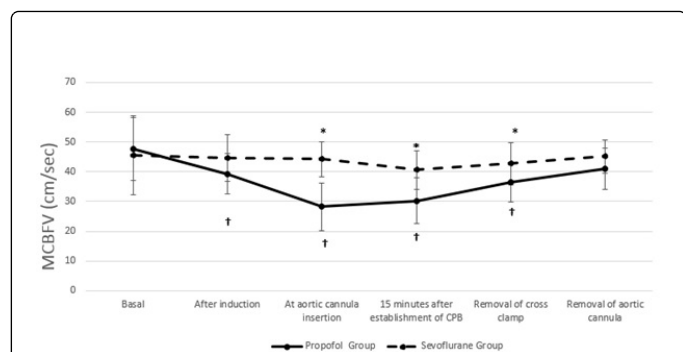


Figure 2: Mean Velocity (cm/s) of middle cerebral blood flow in the studied groups. Data are in mean \pm SD, *P<0.05 Significant when compared with the propofol group; † P<0.05 Significant when compared with the basal value in the same group.

The average number of embolic events detected within 180 second following every event were higher in sevoflurane group when compared to propofol group at insertion and removal of aortic cannula as well as on release of aortic cross clamp (Figure 3).

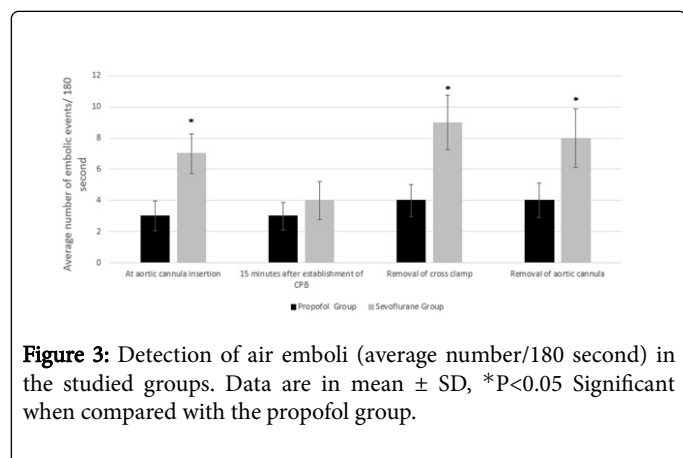


Figure 3: Detection of air emboli (average number/180 second) in the studied groups. Data are in mean \pm SD, *P<0.05 Significant when compared with the propofol group.

Cerebral oxygen saturation showed no differences between both groups throughout the surgery (Figure 4).

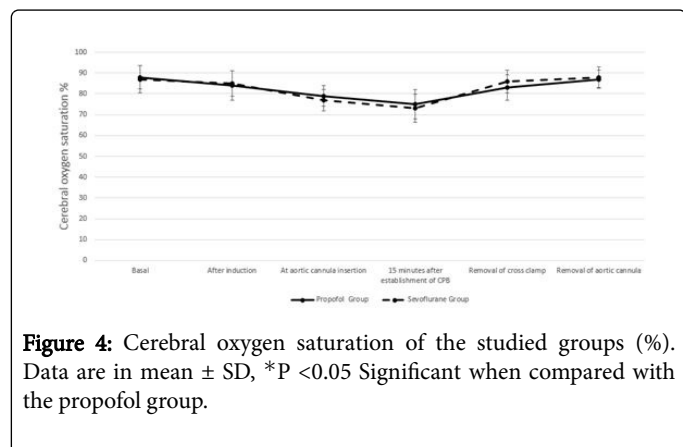


Figure 4: Cerebral oxygen saturation of the studied groups (%). Data are in mean \pm SD, *P < 0.05 Significant when compared with the propofol group.

The mean average of Mini-Mental State Examination results statistically insignificant between both groups. However the mean

value was slightly lower after one week of surgery and improved by time to be almost near normal three months after surgery in both groups (Table 3).

	Propofol Group	Sevoflurane Group	P Value
Before surgery	34.2 \pm 1.79.63	34.77.55 \pm 1.38	0.55
1 week after surgery	32.37 \pm 2.55	32.90 \pm 2.56	0.849
3 months after surgery	34.54 \pm 1.83	36.76 \pm 2.26	0.279

Table 3: Neuro-cognitive function assessment results of the studied groups. Data are in mean \pm SD.

Discussion

Maintenance of sufficient cerebral blood flow is fundamental for cerebral oxygenation and neurological function [31]. Neurological brain affection during cardiac surgery can be caused by air bubbles when enter the cerebral circulation intra-operatively [5]. Anesthetic agents are considered as a part of pharmacological preventive measures against air bubbles and brain protective effects.

In this study, all patients in propofol anesthesia group showed significant reduction in the number of embolic events and mean cerebral blood flow velocity (CBFV) more than patients in sevoflurane anesthesia group. In addition the mean arterial blood pressure was significantly lower in propofol group than sevoflurane group. There were no differences between the two groups as regard cerebral oxygen saturation and the postoperative neurocognitive function outcome.

According to this study, low incidence of cerebral air emboli, lower cerebral blood flow velocity and MAP were associated with propofol based anesthesia when compared to sevoflurane group.

The lower incidence of embolic events in propofol group than sevoflurane group can be explained by different mechanisms; (1) the Vasoconstrictor effect of propofol on small arterioles in cerebral circulation. This propofol mediated vasoconstrictor effect increases the resistance force inside small arterioles in arterial side which hinder the smooth passage of foreign materials into cerebral circulation [32]. (2) Propofol causes reduction in CBF which decreases the cerebral regional blood flow with subsequent attenuation of the carrying power and driving force of blood flow to foreign objects including air emboli [32, 33]. (3) The reduction in cerebral blood flow velocity caused by propofol within the cerebral arterial tree can be explained by decreasing the cerebral metabolic rate of oxygen, and suppressing effect on endothelium-dependent relaxation that might reduce the steady-state CBF velocity [34,35]. Third mechanism is the definitive effect of Propofol on MAP. Propofol is known to decrease MAP. This leads to decrease the driving force of blood flow associated with lower its carrying ability. This is attributed to decrease in SVR, negative inotropic effect, and resetting of baroreceptors caused by propofol [33,35,36].

These combined propofol actions results in reducing cerebral exposure to the embolic load during high risk events in cardiac surgery such as aortic cross clamping, partial cross-clamping, cross-clamp removal, or resumption of cardiac ejection that commonly occurs on weaning of CPB [32].

On the other hand, a higher load of air emboli was noticed in sevoflurane group. All volatile anesthetic agents cause direct cerebral vasodilatation to different degrees. Desflurane and sevoflurane are

more potent cerebral vasodilator than other volatile agents. This vasodilatation with loss of autoregulation decreases the vascular resistance to blood flow with any foreign objects inside. Also sevoflurane increases cerebral metabolic rate with associated increase changes in the global and regional blood flow as well. In addition, sevoflurane maintains MAP with maintenance of the driving force of blood flow to all organs including the brain [37-39]. Sevoflurane is not associated with increases in heart rate, whereas increasing concentrations of sevoflurane slightly decrease blood pressure, myocardial contractility and reduces baroreflex function [40].

In the current study, CBFV was decreased between 13-17% by propofol effect. This study is very similar to the work published by Panel et al., in which the impact of propofol infusion (6 mg/kg/h for 40 min) on CMRO₂ was evaluated. He observed a reduction in CBF and CMRO₂ with propofol without affecting arteriovenous oxygen delivery, suggesting maintenance of normal cerebral circulation and metabolism [41].

In another study by Newman et al., he tried to evaluate the embolic preventive and brain protective effect of propofol. He did not define a fixed rate for propofol infusion but took an 80% suppression of EEG as a target point and he reported reduction of cerebral blood flow, embolic exposure, cerebral oxygen delivery and metabolic rate both in normothermia and hypothermia [32].

This findings also agree with previous research published on the effect of propofol on cerebral hemodynamics. Radhika et al. compared the effect of anesthesia induction using IV etomidate 0.2 to 0.6 mg/kg or propofol 1 to 2.5 mg/kg at induction on middle cerebral artery flow. He reported that propofol decreases the cerebral blood flow velocities and perfusion pressure with preserved cerebral autoregulation [42].

Also, Eng C in his study concluded that propofol causes cerebral vasoconstriction. He induced his anesthesia with propofol 2.5 mg.kg⁻¹ bolus followed by continuous infusion of 150 micrograms.kg⁻¹.min⁻¹ [43].

Regarding sevoflurane, cerebral blood flow was increased by only 1-2%. Kuroda, et al. in his study proved that sevoflurane has cerebral vasodilator effect and can increase CBFV and embolic load which matches the present study [44]. Previous reports indicated that sevoflurane between 0.5-1.0 MAC has minimal vasodilating effect on small brain arterioles and has no systemic hemodynamic effects at the most common used 1 MAC sevoflurane [40, 45].

In our study, CBFV was lower in propofol group relative to sevoflurane group. Similarly, previous work by Kaike, et al., has assessed the effect 1 MAC, 1.5, and 2 MAC of sevoflurane and 0 µg/ml, 6 µg/ml, 9 µg/ml, and 12 µg/ml TCI of propofol on regional cerebral blood flow on volunteers. He reported that both anesthetics medications caused a global decrease of rCBF however this reduction was greater in propofol more than sevoflurane [46].

Kaisti, et al. in their study comparing effects of sevoflurane, propofol, and adjunct nitrous oxide on regional cerebral blood flow, oxygen consumption, and blood volume in humans by using positron emission tomography tracers, reported that propofol reduced rCBF more than sevoflurane but reduces rCMRO₂ only to an extent similar to sevoflurane [47]. Another study by Engelhard found that propofol caused cerebral vasoconstriction, intact cerebrovascular autoregulation and maintained CO₂ reactivity. On the other hand sevoflurane caused cerebral vasodilatation, decreased CPP, impaired cerebrovascular

autoregulation and maintained CO₂ reactivity; and hence supporting our findings [48].

Regarding cerebral oxygen saturation, it showed no significant differences between both groups throughout the study. In contrary to our findings, significant lower rSO₂ values were reported in propofol group used during gynecological operation in relation to sevoflurane group. In this study, the effect of propofol and sevoflurane on rSO₂ was evaluated only during anesthesia induction however, in our study we evaluated propofol and sevoflurane effect on rSO₂ throughout the whole surgery [49]. In this study, we hypothesize that propofol would be associated with better neurological outcome than sevoflurane, however the results showed no significant differences in neurocognitive outcome between propofol and sevoflurane groups. This may be attributed to the facts that propofol decreases cerebral embolic events, conserve cerebrovascular autoregulation regardless metabolism and mitigates intracranial pressure. [50-52]. In addition propofol can attenuate glutamate-mediated excitotoxic mechanisms by either decreasing NMDA receptor activation, reducing glutamate release, or increasing glutamate uptake into neuronal and glial cells. In also potentiates GABAergic neuronal activity, [53] and has antioxidant activity [54].

Meanwhile, sevoflurane exhibits its neuroprotective effect by a dose dependant reduction in cerebral metabolic requirements, or related to decreased apoptotic cell death in the post-ischemic period [55,56]. Alteration of body temperature during cooling on CBP that decreased the CMRO₂, changes in PaCO₂ that may affect CBF and autoregulation mechanisms and small size of microemboli (less than 200 micron) that was not large enough to occlude the small arterioles [57]. In a recent study, sevoflurane proved to improve the cerebral oxygenation in comparison to propofol however, both sevoflurane and propofol have insignificant effect on postoperative neurocognitive function in short term outcome [58].

Conclusion

In comparison to sevoflurane, propofol decreases the incidence of cerebral air embolic events, mean cerebral blood flow velocity and MAP to a great extent than sevoflurane. Meanwhile, it has equivalent effect to sevoflurane regarding regional cerebral oxygen saturation and neurocognitive outcome.

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