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The Effect of Propofol versus Etomidate Induction on Middle Cerebral Artery Flow Velocities and its Derived Parameters Using Transcranial Doppler Ultrasonography

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Abstract

Background: Transcranial Doppler Ultrasonography (TCD) is a valuable noninvasive addition to comprehensive neurological monitoring. Our objective is to compare the effect of intravenous propofol *vs* etomidate induction on middle cerebral artery (MCA) flow velocities and its derived parameters, as measured by TCD evaluation in patients undergoing surgery for intracranial tumors.

Material and Methods: Forty patients aged 15 to 70 years, with intracranial space occupying lesions (SOL) posted for craniotomy and excision of SOL were randomly selected to receive intravenous propofol or etomidate during induction of anaesthesia. A RIMED DIGI-LITE TCD system (software version 1.17.5.5) was used to insonate the MCA on the non-tumor side. Patients vitals including mean arterial pressures (MAP) and MCA flow velocities (peak systolic, diastolic and mean) were measured at pre induction and at 1 min, 3 min, 5 min, 10 min and 30 min after induction. The pulsatility (PI) and resistivity (RI) indices and transient hyperemic response ratio (THRR) were derived and the above were compared with their preinduction/awake values. Results: Within a MAP range of 50 to 120 mm Hg, propofol induced a significant fall in MCA flow velocities (21.6 ± 32%; p-value=0.001). There was no significant change in flow velocities during intubation with the use of either drug. The PI increased significantly at the time of intubation in both the groups. The mean PI was raised with propofol [1.26 ± 0.42 (p-value=0.036)] as well as with etomidate [1.41 ± 0.38 (p-value=0.006)]. There was a significant fall in estimated cerebral perfusion pressure after propofol induction but not with etomidate. No significant change in the Transient Hyperemic Response Ratio was seen in either of the two groups.

Conclusion: Propofol decreases cerebral blood flow velocities and perfusion pressure. Etomidate provides stable hemodynamic parameters, flow velocities and perfusion pressures. Both drugs preserve cerebral autoregulation and provide good intubating conditions in patients with intracranial tumors.

Keywords: Transcranial doppler ultrasonography; Middle cerebral artery flow velocity; Pulsatility index; Resistivity index; Transient hyperemic response ratio; estimated cerebral perfusion pressure; Propofol; Etomidate.

Introduction

Brain tumors are second only to stroke as a cause of death from neurologic disease. Concerns unique to induction of anaesthesia for craniotomy are related to Intra Cranial Pressure (ICP) in the case of mass lesions and prevention of hemorrhage in the cases of vascular lesions. The question of suitability of anaesthetic agents, especially in the context of unstable ICP, arises often. In general, intravenous anesthetics decrease cerebral metabolic rate for oxygen (CMR) and cerebral blood flow (CBF) in parallel fashion, whereas most inhalational anesthetics decrease CMR with an increase in CBF [1]. The coupling of CMR and CBF is better maintained with intravenous anesthetics, whereas it is lost with inhalational anesthetics at high concentrations. Propofol and etomidate are both excellent agents for neuroanaesthesia. Previous research has shown that each anaesthetic is similar in the neuroprotective effects on ICP, CBF and CMR [2]. Transcranial doppler (TCD) ultrasonography is a real-time, non-invasive technique which allows us to observe velocity, direction and properties of blood flow in the cerebral arteries by means of a pulsed ultrasonic beam. It has widely been used to investigate cerebral blood flow velocity and indirectly, changes in cerebral blood flow [3]. The goals of this study were to compare the effects of propofol and etomidate on middle cerebral artery flow velocities, its derived parameters and on cerebral autoregulation during induction of general anaesthesia, in patients with intracranial space occupying lesion, using Transcranial Doppler Ultrasonography.

Methods

After Institutional Ethical Committee clearance, this prospective, randomized, double blinded study was conducted over a period of two years. For the power of study of 0.8, 40 ASA class 1 and 2 neurosurgical patients of either sex, aged 15 to 65 years, with unilateral intracranial space occupying lesion and no previous history of radiotherapy were included in our study. Patients with bilateral lesion, revision surgery history of stroke, carotid stenosis, meningitis, and intracranial bleed, cardiac, pulmonary, endocrine or renal disease were excluded from our study.

After taking an informed written consent, the patients were randomly allocated into the following groups, using a computer generated random number table:

Group E: Patients received IV. Etomidate 0.2 to 0.6 mg/kg at induction.

Group P: Patients received IV. Propofol 1 to 2.5 mg/kg at induction.

The group assigned was enclosed in a sealed opaque envelope. An anesthesiologist not involved in the study, prepared and administered the drug, according to randomization. The observer who collected the intra-operative data as well as the operating surgeon was blinded to the drug administered.

The RIMED DIGI-LITE Transcranial Doppler system (software version 1.17.5.2) was used to insonate the middle cerebral artery (MCA) on the non-tumor side. The 2MHz hand held ultrasound probe was placed in the temporal window. TCD signals of the MCA once obtained were verified by a brief compression of the ipsilateral common carotid artery. The signal was traced till the internal carotid artery bifurcation at a depth of approx. 60-65 mm. The depth of insonation was then reduced to find the proximal portion of the MCA trunk. MCA flow velocities obtained at depth 45 to 55mm were included in the study.

Cerebral autoregulation was measured by Giller's transient hyperemic response (THR) test. For this the MCA systolic velocities were measured for five heart cycles ending with the one preceding carotid compression. The mean value of systolic peaks from these five heart cycles was denoted (FV1). The ipsilateral common carotid artery was then compressed for 5 to 9 seconds. The MCA systolic velocities of two heart cycles after release of compression, excluding the first cycle, were recorded and their mean was denoted (FV3). The transient hyperemic response ratio (THRR) is a quantitative index to evaluate the autoregulation state. It is defined as the ratio (FV3)/ (FV1) [4].

After recording the baseline parameters and performing the baseline autoregulation test, induction of anaesthesia was done as mentioned above. Both groups received premedication with midazolam IV, opioid analgesia with butorphanol 0.03mg/kg IV and vecuronium bromide 0.1mg/kg was used for muscle relaxation in both groups. Both groups received titrated doses of IV propofol or etomidate, depending on their randomization. The end point of induction was loss of verbal contact with the patient. At 3 min of injection of muscle relaxant, each patient was intubated and given an air-oxygen mixture and maintenance dose of IV anaesthetic was infused. Intermittent positive pressure ventilation was set to achieve an end-tidal CO_2 of 30 to 40 mm Hg. Patients vitals and Doppler parameters were measured before and at 1, 3, 5, 10, and 30 min after induction of anesthesia. Cerebral autoregulation was again measured again at 30 min of induction of anaesthesia.

All patients were observed for the following parameters:

Clinical parameters:

- Heart rate (HR)
- Pulse oximetry (SpO_2)
- Mean arterial pressure(invasive)(MAP)
- End tidal carbon dioxide ($EtCO_2$)

TCD parameters:

- Peak Systolic MCA flow velocity (FVsys)
- End Diastolic MCA flow velocity (FVdia)
- Mean MCA flow velocity (FVmean)
- Gosling's Pulsatility Index (PI) FVsys - FVdia / FVmean
- Pourecelot's Resistivity Index (RI) FVsys - FVdia / FVsys
- Transient hyperemic response ratio (THRR) FV3/FV1
- Estimated cerebral perfusion pressure (eCPP)= FVmean x (BPm-BPd)/(FVm-FVd)

Statistical analysis

Data was analyzed using software SPSS ver. 16. The results were expressed as mean ± standard deviation. Students paired t tests were used to compare the means of hemodynamic and Doppler parameters between two consecutive measurements within the same group. Pearson correlation coefficients were calculated to evaluate the relation between changes in MAP, FVsys, FVdia, FVmean, PI, RI and eCPP within the group. A p value of less than 0.05 was considered significant and that of less than 0.01 was highly significant.

Results

The demographic profile of the two groups was similar in age but the etomidate group had fewer posterior fossa lesions and fewer women (Table 1). All patients received perioperative dexamethasone therapy for management of cerebral edema. The mean induction dose for propofol was 2.11 ± 0.50 mg/kg and that for etomidate was 0.29 ± 0.038 mg/kg (Table 2).The mean End tidal CO_2 values in the propofol group were 32.15 ± 2.76 and those for the etomidate group were 32.66 ± 2.68 There was a decrease (9.6 ± 34%) in mean Heart rate (HR) over baseline after propofol induction which was significant (p-value=0.008). HR at 5 min 10 min and 30 min of induction also decreased significantly from baseline (p-value=0.017, 0.001, 0.019 respectively). There was no significant change in HR after etomidate induction and the mean HR increased by 2.0% over baseline which was not significant. There was no significant change in HR during intubation at 3 min in either of the groups (Figure 1). The mean arterial pressure (MAP) decreased by (13.9 ± 16) % from baseline at 1 min of induction with propofol which was significant (p-value=0.002). There was an insignificant increase in MAP after intubation at 3 min of propofol induction after which it remained stable with fluctuations of less than 5% of its preinduction values. The MAP values in the etomidate group showed no significant change from baseline (Figure 2). The systolic flow velocities (FV sys) decreased significantly after induction with propofol and remained low throughout the study. The mean (Fsys) showed a fall of (17 ± 44%) from baseline (p-value=0.001). No significant change in FVsys was seen after etomidate induction. The diastolic flow velocities (Fvdia) showed a similar fall after propofol induction .The mean Fvdia decreased by (20 ± 57%) from baseline (p-value=0.012). There was no significant change in Fvdia after etomidate induction. The mean flow velocities (FVmean) also decreased significantly after propofol induction (21.6 ± 32%; p-value=0.001). There was no significant difference in FVmean after etomidate induction. There was no significant change in flow velocities during intubation after administration of either drug (Figure 3). The Resistivity index (RI) increased significantly at 5 min after induction with

Table 1: Demographic profile

	Variable characteristics	Propofol Group	Etomidate Group
Age (yrs)	≤ 40	12	14
	>40	8	6
Sex	Male	11	18
	Female	9	2
Weight (kg)	≤ 50	5	3
	>50	15	17
Intracranial Pathology	Meningiomas	6	7
	Gliomas	8	11
	Posterior fossa SOL	6	2

Table 2: Mean dose range

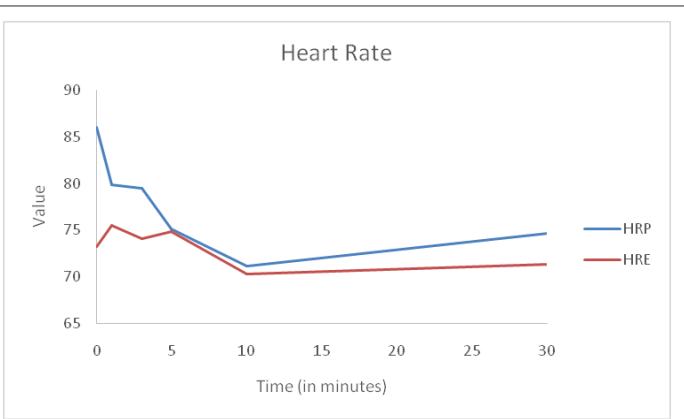| Characteristic	Mean ± SD	Range
Weight (kg)	56.75 ± 14.14	25 – 85 (60)
Dose Propofol (mg/kg)	2.1095 ± 0.505	1.0 – 2.8 (1.8)
Dose Etomidate (mg/kg)	0.29 ± 0.038	0.2 – 0.48(0.31)

Figure 1: Line Diagram showing variation of Heart Rate with Propofol (HRP) and Etomidate (HRE) induction over time.
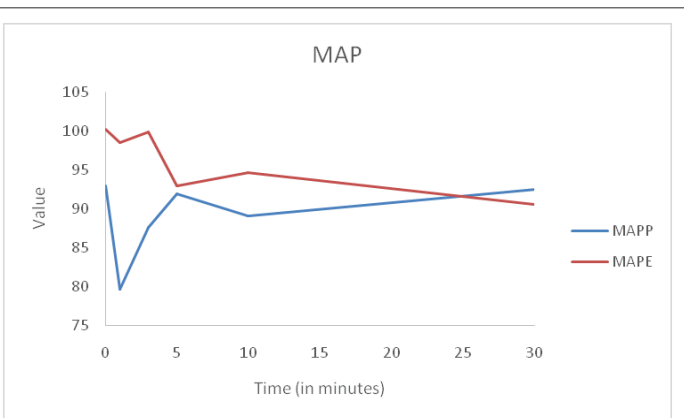

Figure 2: Line Diagram showing variation of Mean Arterial Pressure with Propofol (MAPP) and Etomidate (MAPE) induction over time**.**
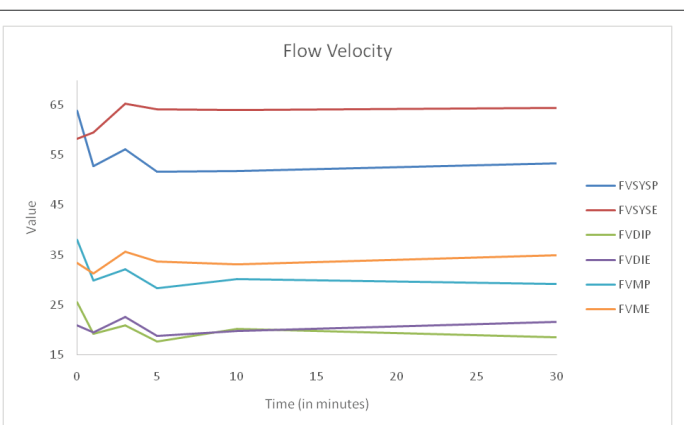

Figure 3: Line Diagram showing variation of Flow Velocity Systolic with Propofol (FVSYSP) and Etomidate (FVSYSE), Flow Velocity Diastolic with Propofol (FVDIP) and Etomidate (FVDIE) and Flow Velocity Mean with Propofol (FVMP) and Etomidate (FVME) induction over time.

propofol (p-value=0.035) after which it returned to normal values. This is suggestive of intubation induced increase in cerebral vascular resistance. The RI values after etomidate induction also increased significantly at 5 min of induction (p-value=0.002) and remained significantly raised thereafter the mean RI was (0.65 ± 0.14) which is within the normal range. The Mean RI was significantly higher than baseline. (p-value=0.009). The Pulsatility

Index (PI) was not significantly changed till 5 min after induction with propofol. At 5 min the PI value increased significantly (1.41 ± 0.62; p-value=0.017). However there was no significant change in PI thereafter. Although the mean PI remained significantly increased throughout (1.26 ± 0.42; p-value=0.036). There was a significant rise in PI after etomidate induction throughout the study. The mean PI in the etomidate group was (1.41 ± 0.38; p-value=0.006) which is above the normal range of (0.6 to 1.1) (Figure 4)**.** There was a ($13.0 \pm 43\%$; p-value=0.021) fall in estimated Cerebral Perfusion Pressures (eCPP) after propofol induction. The mean eCPP was found to be 53.3 ± 20.65. There was no significant change in eCPP values after etomidate induction. The mean CPP was found to be 47.7 ± 15.14 in the etomidate group **(**Figure 5**)**. The Transient Hyperemic Response Ratio (THRR) did not change significantly in either group which is suggestive of preserved cerebral autoregulation in both groups. The THRR was found to be 1.38 and 1.30 before and after induction with propofol respectively.The etomidate group had THRR values of 1.41 and 1.31 before and after induction.Thus the values appeared nearly similar (Plates 1 and 2)**.** We observed a significant correlation between eCPP and RI in both the groups (p-value<0.001) with a correlation coefficient of -0.49 for propofol and etomidate alike**. (**Table 3, Figure 6a and 6b)**.** There was significant correlation between eCPP and PI in both the groups (p-value <0.001) with a correlation coefficient of -0.39 for propofol and -0.60 for etomidate **(**Table 4, Figure 7a and 7b)**.**There were no instances of post operative hypotension or post operative nausea and vomiting during the two day follow up after craniotomy in either group.
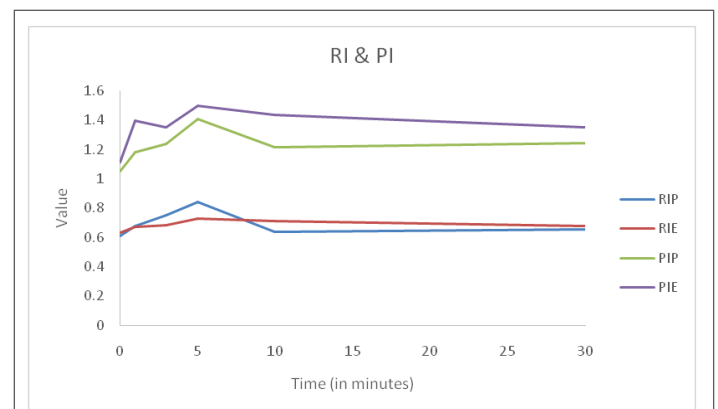

Figure 4: Line Diagram showing variation of Resistivity Index with Propofol (RIP) and Etomidate (RIE), and Pulsatility Index with Propofol (PIP) and Etomidate (PIE) induction over time.
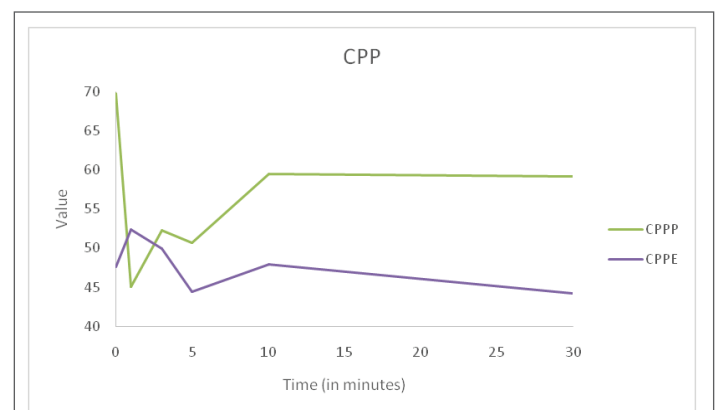

Figure 5: Line Diagram showing variation of Cerebral Perfusion Pressure with Propofol (CPPP) and Etomidate (CPPE) induction over time.
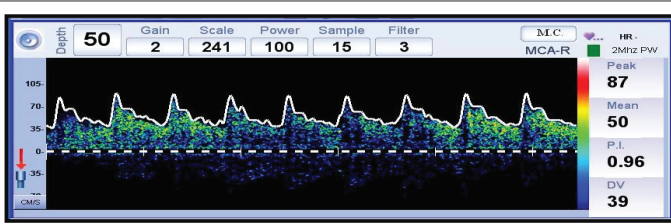
Plate 1: Giller's transient hyperemic response (THR) test (preceding carotid compression)
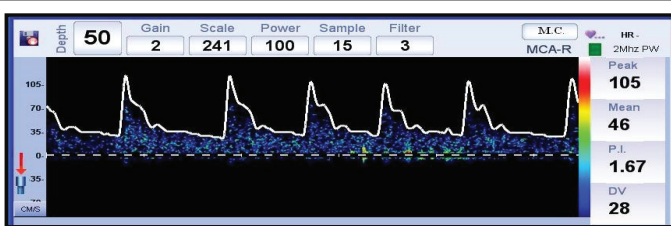

Plate 2: Giller's transient hyperemic response (THR) test (after release of carotid compression)

Table 3: Correlation between Cerebral Perfusion Pressure and Resistivity Index with Propofol vs Etomidate induction

	CPP with RI (Propofol)	CPP with RI (Etomidate)
Correlation coefficient	-0.492	-0.492
p value (sig – 2 tailed)	<0.001	<0.001

Discussion

Patients with intracranial space occupying lesions are in a state of delicate intracranial homeostasis. The choice of anaesthetic agents in craniotomy therefore is biased towards those agents that cause a decrease in ICP, provide a relaxed brain for surgery and maintain the CPP and cerebral autoregulation. The pharmacokinetic properties of propofol make the drug suitable for induction and maintenance of anaesthesia by intravenous infusion [5].

Etomidate is also a potent cerebral metabolic depressant and can be used as an induction agent in patients with hypotension or cardiac disease because it has the advantages of minimal cardiovascular depression [6]. Both these agents have been credited with ICP reduction and cerebroprotective effects [7,8]. They have also been implicated with precipitation of cerebral ischaemia in various studies [9-11].When these pharmacological $CMRO_2$ reducing anesthetic agents are given for brain protection, their effects should be assessed with continuous or intermittent monitoring of cerebral blood flow. We used intermittent Transcranial Doppler monitoring of middle cerebral artery flow velocities in our study.

Mishra et al. [12] noted a significant decrease in both mean arterial pressure (MAP) and heart rate (HR) when midazolam and butorphanol were administered to patients before induction of general anaesthesia with propofol. In our study; there was a similar significant fall in HR and MAP after induction with propofol which was not seen in the etomidate group.

Transcranial Doppler Ultrasonography (TCD) can provide continuous beat-to-beat measurements of cerebral blood flow velocity (CBF) in the basal cerebral arteries with a high temporal resolution. Aaslid, Markwalder and Nornes in their landmark study postulated that the TCD measured velocity in the MCA, ACA, and PCA was 62 ± 12, 51 ± 12, and
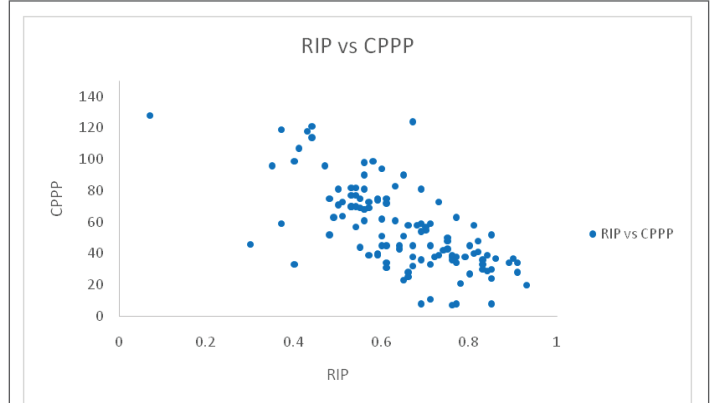

Figure 6a: Scatter Diagram showing the correlation between Cerebral Perfusion Pressure and Resistivity Index with Propofol induction. (3 data points are more than 1. Termed as outliers, they are not shown in the graph)
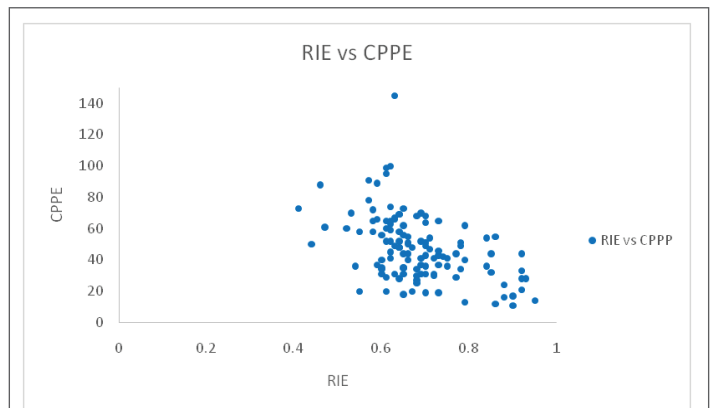CPPP: Cerebral Perfusion Pressure with Propofol; RIP: Resistivity Index with Propofol.

Figure 6b: Scatter Diagram showing the correlation between Cerebral Perfusion Pressure and Resistivity Index with etomidate induction.
CPPE: Cerebral Perfusion Pressure with Etomidate; RIE: Resistivity Index with Etomidate.

Table 4: Correlation between Cerebral Perfusion Pressure and Pulsatility Index with Propofol vs Etomidate induction

	CPP with PI (Propofol)	CPP with PI (Etomidate)
Correlation coefficient	-0.398	-0.607
p value (sig – 2 tailed)	<0.001	<0.001

44 ± 11 cm/sec respectively. They also found that the MCA flow velocity is a function of the diameter of that segment of the vessel as measured by angiography [13]. Stephan et al. [14] did not find changes in the diameter of the MCA after acetazolamide provocation testing with high-resolution MR imaging thus concluding that changes in MCA flow velocity measured by TCD reflect relative changes in cerebral blood flow after acetazolamide provocation testing. Sorond et al. [15] confirmed these findings in their study.

Harrison et al. [16] and Matta et al. [17] have all observed varying degrees of fall in MCA flow velocities after propofol induction. In our study we found a significant fall in systolic diastolic and mean MCA flow velocities after propofol induction.
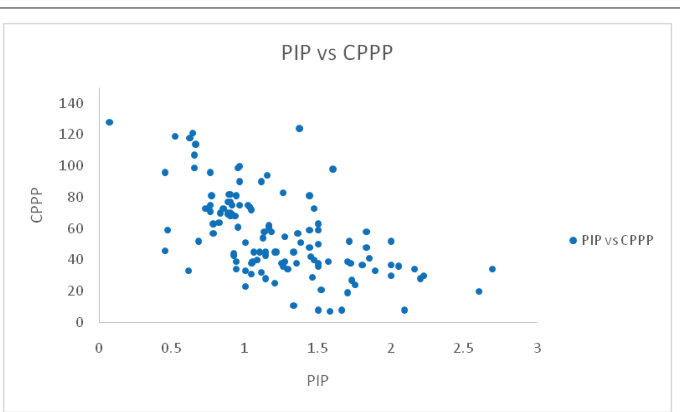
Figure 7a: Scatter Diagram showing the correlation between Cerebral Perfusion Pressure and Pulsatility Index with propofol induction.
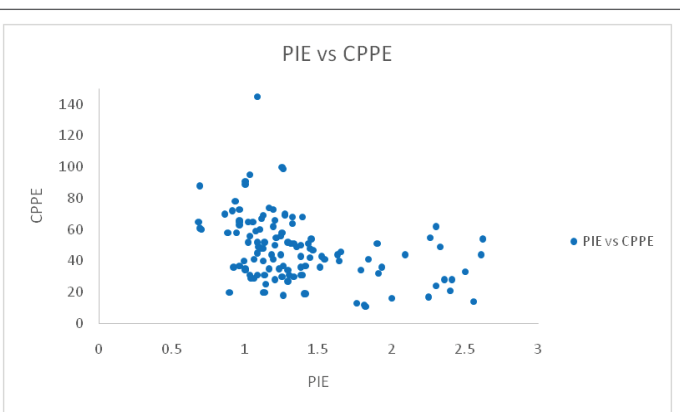CPPP: Cerebral Perfusion Pressure with Propofol; PIP: Pulsatility Index with Propofol.

Figure 7b: Scatter Diagram showing the correlation between Cerebral Perfusion Pressure and Pulsatility Index with etomidate induction.
CPPE: Cerebral Perfusion Pressure with Etomidate, PIE: Pulsatility Index with Etomidate.

There is very limited data on the effect of etomidate on TCD measured flow velocities. Renou et al have noted that etomidate decreased both regional CBF and $CMRO_2$. It was concluded that etomidate is a potent cerebral metabolic depressant [18]. We found no significant change in the systolic diastolic and mean MCA flow velocities after etomidate induction.

The MCA FV waveform observed using TCD is dependent on the arterial blood pressure waveform and the viscoelastic properties of the cerebrovascular bed provided the blood rheology remains constant. Thus, if variables such as MCA diameter and BP remain constant, the pulsatility of blood flow through the conductance vessel reflects distal cerebrovascular resistance. Several indices describing the pulsatility of blood have been formulated; the most commonly adopted is the pulsatility index (PI) of Gosling

Gosling PI = (FVs - FVd)/FVmean

The key advantage of the Gosling PI is that it is dimensionless and therefore independent of sampling techniques, provided the signal-to-noise ratio is good and the gain setting of the instrument is constant. Normal PI ranges from 0.6 to 1.1. PI is a useful indicator of cerebral hemodynamic asymmetry. It is also an indicator of low CPP [19]. Bellner et al. [20] found that independent of intracranial pathology, a significantly strong positive correlation between PI and

intraventricular ICP monitoring with a correlation coefficient of 0.938. Chan et al. [21] reported a correlation (-0.725) between PI and CPP with an even better correlation (-0.942) as CPP decreased below a critical value of 70 mm Hg.

The other index of Cerebral Vascular Reactivity that has been widely used is the resistivity index (RI) described by Pourcelot. The arterial resistance index developed by Leandre Pourcelot is the value of the resistance to blood flow caused by the microvascular bed distal to the site of measurement. It is used in arteries that have no reverse flow. The RI is based on the fact that in a territory, the high resistance of distal vessels produces a low diastolic flow in the artery responsible for blood supply to this area, thus increasing the difference between peak systolic velocity and end diastolic velocity [22].

Pourcelot RI = (FVs-FV) / FVs [23]

In our study we found a statistically significant and sustained increase in both the PI and RI in the etomidate group. There was no significant change in RI in the propofol group where as the mean PI was significantly increased in this group

Aaslid et al. have determined CPP with TCD parameters using the formula:

eCPP=FVm X A1 / F1

(F1=amplitude of the fundamental frequency components of flow velocity and A1=amplitude of the fundamental frequency components of arterial pressure), the fundamental frequency is determined by fast Fourier analysis of the waveform and is equivalent to the heart rate [24].

Belfort et al gave the following formula for estimated CPP calculation.

eCPP=FVmean x (BPm-BPd)/ (FVm-FV) [25].

We used Belfort's formula in our study to estimate the CPP noninvasively and found a significant fall in eCPP after propofol induction but no significant change in eCPP after etomidate induction. The strength of correlation between PI and eCPP in the propofol and etomidate groups was moderate with values of -0.49 and -0.60 respectively.

Harrison and Matta have both concluded that propofol anaesthesia preserves if not improves cerebrovascular reactivity [16,17]. Renou also stated that the cerebrovascular reactivity to carbon dioxide was maintained under etomidate anaesthesia [18]. We used Giller's Transient Hyperemic response test to determine the auto regulatory status of our patients [4]. Our study also concurs that there is no significant change in the transient hyperemic response ratio (THRR) in either of the groups after induction. The THRR ratio remained above 1.09 throughout the study in both the groups suggesting intact autoregulation.

Conclusion

The greatest advantages of TCD are that it is relatively inexpensive, noninvasive, and non-radioactive and it furnishes continuous information about the cerebral circulation. At present, TCD has received Grade C recommendation for perioperative monitoring with level III evidence supporting its use in the perioperative period [26]. Our study shows that the decrease in cerebral flow velocities induced by propofol, persisted even after hemodynamic stability was attained after induction doses of propofol. On the contrary etomidate provided stable hemodynamic parameters as well as stable flow velocities. Both etomidate and propofol were associated with good intubating conditions in patients with intracranial tumors. Both drugs preserve cerebral autoregulation but have the potential to cause cerebral ischaemia.

In conclusion we would like to state that propofol induction causes a greater decrease in flow velocities and eCPP in comparison with

etomidate whereas etomidate induction causes a greater increase in PI and RI as compared to propofol. So elective neurosurgical patients with intracranial SOL can be preoperatively evaluated with Transcranial Doppler Ultrasonography, patients with normal to raised MCA flow velocities and eCPP can be induced with propofol while those with low MCA flow velocities and eCPP can be planned for etomidate induction.

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