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ORIGINAL ARTICLE

Comparison of total intravenous anesthesia vs. inhalational anesthesia on brain relaxation, intracranial pressure, and hemodynamics in patients with acute subdural hematoma undergoing emergency craniotomy: a randomized control trial

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Abstract

Background The major goals of anesthesia in patients with severe traumatic brain injury (TBI) are—maintenance of hemodynamic stability, optimal cerebral perfusion pressure, lowering of ICP, and providing a relaxed brain. Although both inhalational and intravenous anesthetics are commonly employed, there is no clear consensus on which technique is better for the anesthetic management of severe TBI.

Methods Ninety patients, 18–60 years of age, of either gender, with GCS < 8, posted for emergency evacuation of acute subdural hematoma were enrolled in this prospective trial, and they were randomized into two groups of 45 each. Patients in group P received propofol infusion at 100–150 mg/kg/min for maintenance of anesthesia and those in group I received ≤ 1 MAC of isoflurane. Hemodynamic parameters were monitored in all patients. ICP was measured at the dural opening and brain relaxation was assessed by the operating surgeon on a four-point scale (1-perfectly relaxed, 2-satisfactorily relaxed, 3-firm brain, and 4-bulging brain) at the dural opening. It was reassessed at dural closure.

Results Brain relaxation, both at dural opening and closure, was significantly better in patients who received propofol compared to those who received isoflurane. ICP was significantly lower (25.47 ± 3.72 mmHg vs. 23.41 ± 3.97 mmHg) in the TIVA group. Hemodynamic parameters were well maintained in both groups.

Conclusions In patients with severe TBI, total intravenous (Propofol)-based anesthesia provided better brain relaxation, maintained a lower ICP along with better hemodynamics when compared to inhalational anesthesia.

Clinical trial registration Clinical trials registry (NCT03146104).

Keywords TIVA · Inhalational agents · Traumatic brain injury · ICP

Introduction

Patients with severe traumatic brain injury undergoing craniotomy and evacuation of hematoma have a high risk of raised intracranial pressure (ICP). The major goals of

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anesthesia in these emergency neurosurgical procedures are the maintenance of hemodynamic stability, optimal cerebral perfusion pressure (CPP) (60–70 mm of Hg), reduction of cerebral metabolic rate ($CMRO_2$), lowering ICP, and providing a relaxed brain [1]. Although both inhalational and intravenous anesthetic regimes have been used, there is no clear consensus on which of the two is better for the surgical management of these patients who are at high risk of increased intracranial pressure [2, 3].

Inhalational anesthetics are employed in neurosurgery as they reduce $CMRO_2$ and cerebral vascular resistance, being potent cerebral vasodilators [2, 4]. At the same time, they also cause an increase in cerebral blood flow (CBF) and raise the ICP [5], as they cause a flow-metabolism uncoupling at a minimum alveolar concentration (MAC) > 1 [6]. The major advantage though of inhalational agents is ease of titration, thereby facilitating maintenance of hemodynamic stability.

Total intravenous anesthesia (TIVA) helps to circumvent the cerebral vasodilatory effects of inhalational anesthetic agents [7]. Propofol is the most widely used agent for TIVA [8], as it produces dose-dependent reduction in CBF and $CMRO_2$ by virtue of its cerebral vasoconstrictive property. It has also been shown to reduce ICP by maintaining flow-metabolism coupling [9–12]. However, propofol-based TIVA may be difficult to titrate and there is an exaggerated risk of hypotension in bleeding hypovolemic patients [13].

TIVA and inhalational anesthesia, both have been used successfully in elective craniotomies for brain tumors, with acceptable cerebral dynamics [4, 9, 14–21]. To our knowledge, there are no studies comparing these two anesthetic techniques in the setting of emergency craniotomy for severe TBI, particularly with respect to ICP, brain relaxation, and hemodynamic stability.

Our study has been designed as a prospective, randomized controlled trial to compare the effects of TIVA and inhalational anesthetic agents on brain relaxation, intracranial pressure and intraoperative hemodynamics in patients with severe TBI undergoing emergency craniotomy for evacuation of acute subdural hematoma.

Methodology

After obtaining approval from the scientific advisory committee and the Institute ethics committee (IEC no.—JIP/IEC/2016/1103), the trial was registered with the clinical trials registry (NCT03146104). The study was conducted from August 2017 to December 2018. Written informed consent for the purpose of the study was obtained from a legally acceptable representative family member. 90 Patients belonging to the age group of 18–60 years of either sex, with isolated head injuries, with Glasgow coma scale (GCS) < 8 and posted for emergency evacuation of acute traumatic subdural hematoma at our tertiary care neurosciences center were included in the study (Fig. 1). Patients with isolated extradural hematoma, those who did not consent and those decided for conservative management were excluded from the study. The number of patients who were intubated in the emergency department was noted. Patients with GCS motor score of 5, maintaining airway and oxygen saturation, were intubated in the operation theatre after induction of anesthesia. Computer tomography (CT) findings were recorded for all the patients.

In the operation theatre, standard monitors including non-invasive blood pressure (NIBP), electrocardiogram (ECG), and pulse oximetry were attached and a 16G/18G intravenous cannula was secured in one of the limbs. Randomization was done using block randomization with varying block sizes generated through a computer program and allocation was done using a sealed envelope technique. All the non-intubated patients were pre-oxygenated with 100% oxygen for 3 min. The anesthesia was induced with 3 mcg/kg fentanyl and 2 mg/kg propofol. Muscle relaxation was achieved with 0.1 mg/kg vecuronium, and after 3 min of gentle mask ventilation, patients were intubated with an appropriate sized endotracheal tube (8.0 for male and 7.0 for female). Patients who were received intubated were given 3 mcg/kg of fentanyl, 2 mg/kg of Propofol and 0.1 mg/kg of vecuronium. One of the radial arteries was cannulated with a 20G cannula and zero pressure adjustment was done at mid-axillary line for continuous blood pressure monitoring. A 7 Fr. central venous catheter was inserted into the subclavian or internal jugular vein in all the patients. Cardiac output monitor (EV1000) was connected to the arterial and central lines, and values of stroke volume (SV), stroke volume variation (SVV), systemic vascular resistance (SVR), and cardiac output (CO) were obtained.

Anesthesia was maintained with either propofol 100–150 mcg/kg/min (Group P), or isoflurane ≤ 1 MAC (Group I), in a mixture of oxygen and air to maintain FiO2 of 40%. Inj Fentanyl 1 mcg/kg hourly and Inj. Vecuronium 2 mg boluses every 30 min were repeated throughout the surgery. In both, the groups $EtCO_2$ was maintained at 30–34 mmHg and heart rate (HR) and invasive blood pressure (IBP) were maintained within 20% of the baseline value. All patients received normal saline 2 ml/kg/h for maintenance and 1 g/kg of Mannitol at skin incision over a period of 20 min [3]. If the systolic blood pressure dropped more than 20% from baseline, crystalloids were administered initially followed by titration of anesthetic agents, and if the hypotension persisted, vasopressors, either phenylephrine or dopamine was administered.

Upon creation of the first burr hole, a 22G/0.8 mm cannula was placed under the dura and connected to a pressure transducer system zeroed at the level of mastoid process, via a polyethylene catheter [9]. ICP was measured

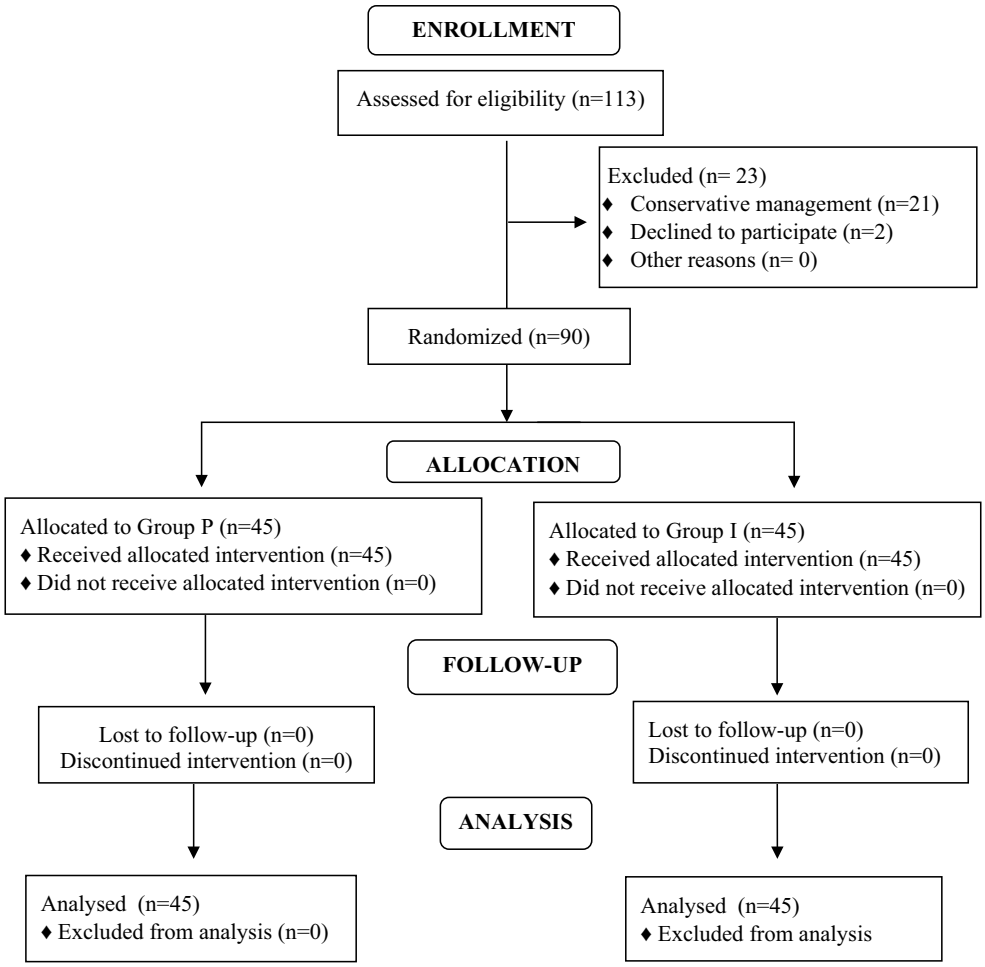

Fig. 1 CONSORT flow diagram for the present study

after confirming the waveforms stabilized over a period of 1 min and the CPP was calculated as the difference between mean arterial pressure (MAP) and ICP. Thereafter, the catheter was removed and the dura was opened at which time the brain relaxation score was assessed on a four-point scale [(1) perfectly relaxed, (2) satisfactorily relaxed, (3) firm brain, (4) bulging brain], using tactile evaluation by the neurosurgeon who was blinded to the anesthetic technique employed [22]. If the ICP was more than 22 mmHg, moderate hyperventilation was instituted to achieve an EtCO2 of 25–28 mmHg and additional boluses of mannitol 0.25–0.5 g/kg administered, if needed. Brain relaxation was assessed again at the time of dural closure, and any lax duraplasty and bone flap replacement was recorded.

Hemodynamic parameters such as HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were recorded at induction (0 min), 5-min post-induction, and every 30 min thereafter. The advanced hemodynamic parameters such as CO, SV, SVV, and SVR were noted once the arterial and central lines were connected to their transducers (0 min) and every 30 min thereafter.

Statistical analysis

Statistical analysis was done using SPSS version 19.0 (IBM Corp). Considering a difference of 1 point in brain relaxation score between the groups as significant and assuming significance of 5%, and with the power of 90%, the sample size was calculated to be 25 in each group [22]. We also calculated sample size based on the expected difference in the subdural pressure. By assuming a level of significance of 5% and power of 80%, to expect a minimum mean difference in subdural pressure of 4 mmHg with a standard deviation of 6.8 between the groups, the sample size was calculated to be 45 in each group [9]. Since the calculated sample size based on the secondary parameter was higher, we chose to proceed with this to achieve greater credibility and reproducibility. The distribution of categorical data such as gender, brain relaxation score, and intraoperative events such as the need

for vasopressors, transfusion, lax duraplasty, and bone flap replacement were expressed by frequency (percentages). The comparison of the brain relaxation score between the groups was carried out using the Chi-square test. Other categorical data were compared using the Fischer exact test. Continuous data such as the age of patients, subdural intracranial pressure, hemodynamic parameters, amount of blood loss, and urine output were expressed as mean with standard deviation. Continuous data between the groups were compared using independent student *t* test. All the statistical tests were carried out at 5% level of significance and *p* value less than 0.05 was considered significant.

Results

Total of 90 patients was enrolled in this prospective randomized study, with 45 in each group. The two groups were comparable in terms of demographic parameters (Table 1). The presence or absence of midline shift and its extent, appearance of basal cisterns and presence or absence of contusion on CT was comparable between groups. Eighteen patients in Group P and twenty in Group I were intubated in the emergency medical services department.

Subdural intracranial pressures and the brain relaxation scores were significantly better in patients who received propofol, compared to those who received isoflurane. While the ICP in the Group P was 23.41 ± 3.97 mmHg, it was 25.47 ± 3.72 mmHg in Group I (*p* value 0.01) (Table 2). Similarly, the brain relaxation score was also significantly better in those who received propofol compared to those who received isoflurane (15/26/4/0 vs. 23/22/0/0, *p* value 0.04) (Table 2). Twenty-seven patients in propofol group and 32 patients in the isoflurane group had ICP > 22 mmHg and were managed with aggressive hyperventilation.

The HR, SBP, DBP, and MAP were recorded at induction, 5-min post-induction and at 30-min intervals thereafter (Supplement 1). Both the groups were comparable in terms of all the above-mentioned parameters recorded at induction and at predetermined timepoints thereafter. Advanced hemodynamic parameters like CO, SV, SVV,

Table 2 Comparison of intracranial pressure (ICP) and brain relaxation score (BRS) at the time of dural opening and dural closure between the two groups

	Group I (*n* = 45)	Group P (*n* = 45)	*P* value
ICP (mmHg)	25.47 ± 3.72	23.41 ± 3.97	0.01
BRS- Dural opening			0.04
1—Perfectly relaxed			
2—Satisfactorily relaxed	–	4 (8.88%)	
3—Tight brain	22 (48.88%)	26 (57.77%)	
4—Bulging brain	23 (51.11%)	15 (33.33%)	
BRS mode (min, max)	4 (3, 4)	3 (2, 4)	
CPP at dural opening	57.60 ± 10.23	61.24 ± 13.78	0.15
BRS—dural closure			
1—Perfectly relaxed	4	16	0.01
2—Satisfactorily relaxed	19	16	
3—Tight brain	12	10	
4—Bulging brain	10	3	
BRS mode (min, max)	2 (1, 4)	1 (1, 4)	

ICP intracranial pressure, *BRS* brain relaxation score, *CPP* cerebral perfusion pressure, *mmHg* millimetres of mercury, *I* isoflurane, *P* propofol

Table 1 Comparison of demographic data and CT findings between the two groups

	Group I (*n* = 45)	Group P (*n* = 45)	*p* value
Age (mean ± SD)	40.84 ± 13.67	40.95 ± 14.29	> 0.05
Gender (M/F) n	32/13	38/7	
GCS at admission Mode (Min, Max)	7 (5, 8)	8 (5, 8)	
Patients intubated in EMS	20	18	
Mid line shift			
No	8 (17.77%)	10 (22.22%)	
< 5 mm	16 (35.55%)	10 (22.22%)	
> 5 mm	21 (46.66%)	25 (55.55%)	
Basal cisterns			
Open	11 (24.44%)	12 (26.66%)	
Effaced	32 (71.11%)	29 (64.44%)	
Closed	2 (4.44%)	4 (8.88%)	
Contusion			
Yes	32 (71.11%)	34 (75.55%)	
No	13 (28.88%)	11 (24.44%)	

M/F Male/female, *n* number, *I* isoflurane, *P* propofol, *EMS* emergency medical services

and SVR were monitored throughout the intraoperative period and they were comparable in both the groups at all the timepoints (Supplement 2).

The brain relaxation measured at the end of the surgery was found to be significantly better in those who received propofol compared to those who received isoflurane [3/10/16/16 vs. 10/12/19/4 (n-number of patients), *p* value 0.01] (Table 2). The frequency of bone flap replacement and lax duraplasty was noted in each group and was comparable (Table 3).

We found a significant difference between the two groups with respect to urine output (*p* value 0.02) (Table 4). The urine output was higher in those who received propofol compared to those who received isoflurane (926.67 ± 336.58 ml in Group I vs. 1169.33 ± 612.94 ml in Group P). Both the groups were comparable with respect to peri-operative fluid replacement, the requirement of vasopressors, blood transfusion, and blood loss.

Table 3 Comparison of bone flap replacement and number of patients underwent lax duraplasty between the two groups

	Group I (*n* = 45)	Group P (*n* = 45)	*p* value
Bone flap			0.69
Placed in Abdomen	33 (73.33%)	34 (75.55%)	
Replaced in situ	8 (17.77%)	9 (20%)	
Stored in bone bank	4 (8.88%)	2 (4%)	
Lax duraplasty (*n*)	16 (35.55%)	10 (22.22%)	0.24

I isoflurane, *P* Propofol

Discussion

Ninety patients were enrolled in this prospective, randomized controlled trial. Both the groups were comparable with respect to age, gender distribution, and CT scan findings. The goals of anesthesia in these patients are to reduce secondary brain injury by reducing intracranial pressure, improving brain relaxation and maintaining hemodynamics. Propofol, the most widely used agent for TIVA, produces dose-dependent reduction in CBF and $CMRO_2$ by virtue of its cerebral vasoconstrictive property. It has also been shown to reduce ICP and maintain flow-metabolism coupling. Hence, Propofol-based anesthetic technique may be preferred over inhalational anesthetic agents [23].

Intracranial pressure and brain relaxation scores at the time of dural opening

Patients with severe TBI have a high risk of raised ICP controlling which is of paramount importance when these patients are posted for emergency surgery for evacuation of the hematoma. Hence, the choice of anesthetic technique may play a pivotal role in controlling ICP and providing brain relaxation. We found a significant reduction in ICP at the dural opening in patients who received propofol compared to those who received isoflurane ($p = 0.01$) (Table 2). Similarly, brain relaxation was also better in patients who were anesthetized with propofol ($p = 0.04$) (Table 2). The effect of TIVA vs. inhalational anaesthesia has been studied extensively in patients with brain tumors undergoing elective craniotomies which reveal comparable cerebral dynamics with these techniques [9, 14–21]. In a randomized controlled trial comparing propofol and isoflurane-nitrous oxide-based anesthesia in 68 patients scheduled for elective supratentorial

Table 4 Comparison of other intraoperative parameters between both the groups

	Group I (*n* = 45)	Group P (*n* = 45)	*p* value
Vasopressors			
Yes	9 (20%)	13 (28.88%)	0.46
No	36(80%)	32 (71.11%)	
No. of patients requiring transfusion (%)	15 (33.33%)	13 (28.88%)	0.82
Urine output (ml)	926.67 ± 336.58	1169.33 ± 612.94	0.02
Blood loss (ml)	848.89 ± 247.60	865.56 ± 285.60	0.77
Fluids given (ml)			
Crystalloids	3880 ± 745.16	3966.67 ± 917.75	0.62
Colloids	600 ± 223.60	583.33 ± 204.12	0.90
Blood products given (ml)			
Packed cell	466.67 ± 216.02	420 ± 143.63	0.44
FFP's	600.00 (0) (*n* = 2)	525.00 ± 150.00 (*n* = 4)	0.54

I isoflurane, *P* Propofol, *ml* millilitres

tumor surgery, Santra et al. did not find any difference in intracranial pressure and brain relaxation after dural opening, between the two groups of patients [18]. In another study comparing three anesthetic techniques—propofol/fentanyl, isoflurane/nitrous oxide, and fentanyl/nitrous oxide, for the maintenance of anesthesia in 121 adults undergoing elective craniotomy for supratentorial masses, Todd et al. did not find any effect of the choice of anesthetic agents on perioperative outcomes [15]. Although the ICP difference was statistically insignificant, more patients in the group which was exposed to isoflurane had ICP greater than 24 mm of Hg, compared to those in the other two groups. However, these studies were conducted in patients posted for elective craniotomies. However, our study included patients with severe traumatic brain injury, who were at risk of elevated ICP. While similar measures were adopted to reduce cerebral edema in both the groups in our study, we found that the intracranial pressure at the dural opening was significantly lower in those who received propofol. We chose to measure the ICP at the subdural level, because being an estimate of regional changes in ICP, it is more sensitive to the presence of space-occupying lesions (tumor or hematoma), compared to being measured at other locations [24, 25]. While other studies have measured ICP at different sites, subdural pressure has been found to be satisfactorily accurate [15, 16].

Brain relaxation at dural closure

The better brain relaxation profile that was noted at the dural opening in patients who received TIVA was sustained until dural closure (Table 2). The brain relaxation after the evacuation of hematoma decides further intraoperative surgical management in terms of lax duraplasty or bone flap replacement. Bastola et al. did not find a significant difference in brain relaxation at different timepoints between propofol and inhalational agents. In our study, despite the difference in brain relaxation after hematoma evacuation between the two groups, we did not find a difference in the performance of lax duraplasty or bone flap replacement (Table 3). The decision to either perform a lax duraplasty or to replace the bone flap at the end of the surgery was left to the discretion of the operating surgeon, taking multiple factors into consideration including the anticipated postoperative course of the patients in the neurotrauma intensive care unit.

Hemodynamic parameters

Hemodynamics were well maintained in both groups (supplement 1). In a trial comparing propofol and sevoflurane (both used in conjunction with remifentanil), in 50 adults undergoing elective intracranial surgery, Sneyd et al. found that the incidence of hypotension (defined as MAP < 60 mm of Hg) was higher in patients anesthetised with sevoflurane [18]. Since HR, MAP, SBP, and DBP may not reflect true hemodynamic status, we studied advanced hemodynamic parameters (Supplement 2), such as CO, SV, SVV, and SVR. The comparable hemodynamics between the two groups in our study is probably due to the extensive hemodynamic monitoring and targeted fluid therapy to maintain optimal CPP in patients who are already at risk of increased ICP.

Other intraoperative parameters

Amount of blood loss, the total amount of crystalloids, colloids and blood products, the requirement of vasopressors, and blood transfusion were comparable in both the groups. We found that the urine output was higher in those who received propofol for the maintenance of anesthesia (Table 4). Motayagheni et al. [26] found propofol to be a better renoprotective agent by virtue of its antioxidant, immunomodulatory, anti-apoptotic, and ischemic preconditioning ability, thereby offering protection against renal ischemia–reperfusion injury as compared to other anesthetic agents. In addition to the renoprotective effects of propofol, glycerol present in it may have a role in increasing urine output by osmotic diuresis [27]. By reducing cerebral edema, glycerol may also have contributed to better brain relaxation in those who received propofol. However, this requires further investigation.

Our study is unique in that it aims to establish an ideal anaesthetic regimen for optimal management of patients with severe TBI undergoing emergency craniotomy and evacuation of the hematoma. Based on our findings, we suggest that TIVA be used over inhalational anesthetics in these patients.

Limitations

We studied the effects of TIVA and inhalational anaesthetics on ICP, CPP, and brain relaxation in the intraoperative period. We did not correlate these changes to the final neurological outcome of these patients, as there may be multiple confounding factors which can influence the final outcome. In addition, sample size may be small to find significant differences in other parameters such as intraoperative hemodynamics and improved neurological outcomes.

Conclusions

In a protocol-based intraoperative anesthetic management comparing TIVA and inhalational anesthetic agents for severe TBI, TIVA provided better brain relaxation and reduction in ICP compared to inhalational anesthesia. ICP measured at the dural opening was significantly less in the TIVA group and CPP was also better preserved in this

group. Both the anesthetic techniques provided satisfactory hemodynamic conditions. Though the present study shows that a TIVA-based technique is better over an inhalational anesthetic-based regime for intraoperative management in patients undergoing emergency craniotomy for severe traumatic brain injury, further studies are needed to look at long term outcome of these patients.

Author contribution All authors have equally contributed in the preparation of protocol, the conduct of study, and manuscript preparation.

Compliance with ethical standards

Conflict of interest None.

Ethical approval Institute ethics committee IEC no. - JIP/IEC/2016/1103.

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