Original Article

The requirement of propofol for induction of anesthesia in patients with traumatic brain injury determined using bilateral bispectral index and target controlled infusion – An observational cohort study

Seham Syeda, Sonia Bansal, Dhritiman Chakrabarti, V. Bhadrinarayan

Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India

Abstract

Background and Aims: Patients with traumatic brain injury (TBI) frequently require emergency surgery. There is a paucity of literature with regard to anesthetic requirements in these patients. The aim of the study was to compare the dose of propofol required for induction of anesthesia in patients with different grades of TBI.

Material and Methods: This prospective, observational study included patients with mild, moderate, and severe grades of TBI undergoing emergency surgery within 48 h of injury. Bispectral Index (BIS) values were recorded using a bilateral BIS sensor. Anesthesia was induced with a target controlled infusion (TCI) pump. Once BIS reached 40, plasma (Cp) and effect-site (Ce) concentration and total dose of propofol required were noted from the TCI pump.

Results: Of the 96 patients recruited, 27, 36, and 33 patients belonged to mild, moderate, and severe TBI (sTBI) groups, respectively. The Ce of propofol in mild, moderate, and sTBI groups was 6 ± 0.9, 5.82 ± 0.98, and 4.48 ± 1.5 μg/mL ($P < 0.001$), and the dose of propofol required was 1.9 ± 0.2, 1.8 ± 0.4, 1.41 ± 0.5 mg/kg, respectively ($P < 0.001$). Baseline BIS on the injured side was 80 ± 7.8, 71 ± 9.4, 55 ± 11.6, and on the uninjured side was 89 ± 5.5, 81 ± 8.4, and 65 ± 12 in mild, moderate, and sTBI groups, respectively.

Conclusions: The requirement of propofol was reduced in patients with sTBI. The dose of propofol required for induction of anesthesia as determined using Ce was significantly lower only between sTBI and mild TBI and not between patients with sTBI and moderate TBI or between mild and moderate head injury. BIS values were significantly different between the groups (highest in mild TBI and lowest in sTBI) and between normal and injured sides within each group.

Keywords: Anesthesia induction, BIS, propofol, target-controlled infusion, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a major global public health concern, contributing significantly to mortality, morbidity, and functional disability. In a retrospective study in the Indian subcontinent of 1527 patients of moderate and severe TBI (sTBI), 34.6% died in the hospital, and among the survivors, 15.72% had a good recovery at 6 months.[1]

Patients with TBI frequently present for emergency surgery, and the need for the anesthetic drug required for induction

Address for correspondence: Dr. Sonia Bansal,
Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru – 560 029, Karnataka, India.
E-mail: itz.sonia77@gmail.com

Access this article online

Quick Response Code:

Website: https://journals.lww.com/joacp

DOI: 10.4103/joacp.joacp_216_21

How to cite this article: Syeda S, Bansal S, Chakrabarti D, Bhadrinarayan V. The requirement of propofol for induction of anesthesia in patients with traumatic brain injury determined using bilateral bispectral index and target controlled infusion – An observational cohort study. J Anaesthesiol Clin Pharmacol 2023;39:208-14.

Submitted: 04-May-2021 **Revised:** 12-Jul-2021
Accepted: 13-Jul-2021 **Published:** 14-Jan-2022

of general anesthesia in patients with TBI is of considerable interest. Studies have demonstrated a decreased requirement of propofol in patients with brain tumors ≥30 mm in size (with mass effect) compared to patients with small tumors and non-neurological patients.[2] Anesthetic requirement is often presumed to be reduced in patients with sTBI when compared to mild and moderate head injury, however, there is the absence of literature regarding the anesthetic requirement.

This study was conducted to evaluate if patients with different grades of TBI undergoing emergency surgery have different drug requirements. The dose of propofol required for induction of anesthesia based on plasma (Cp) and effect (Ce) site concentration using a target controlled infusion (TCI) pump (Orchestra Base Primea-Fresenius Kabi, France) was studied.

Routinely used endpoints for induction of anesthesia such as loss of verbal response, loss-of-eyelash reflex, yawning, and transient apnea are difficult to assess in patients with TBI. Electroencephalogram (EEG)-based parameters like Bispectral Index (BIS) and Spectral Entropy would be more reliable for assessing the endpoint of induction. In this study, we used a bilateral BIS monitor (Covidien IIc, Mansfield, MA, USA) to determine this endpoint.

The primary objective of this study was to compare the dose requirement of propofol for induction of anesthesia in patients with different grades of TBI undergoing surgery (i.e. difference of Cp/Ce between the groups), the endpoint for induction was determined using BIS. Secondary objectives included comparison of baseline BIS on the injured and uninjured side of the brain in different grades of TBI, to determine the difference in propofol requirement in male and female patients with TBI, and to determine the correlation of baseline BIS and postoperative BIS with short-term patient outcome based on extended Glasgow Outcome Scale (GOSE). We hypothesized that the dose of propofol required for induction of anesthesia would be lower in patients with sTBI compared to mild and moderate head injury groups.

Material and Methods

This study was conducted over a period of 16 months in a tertiary care center for neurosciences after obtaining Institutional Ethical Committee approval. Letter no. NIMH/DO/ETHICS/SUB-COMMITTEE (BS & NS) 3rd Meeting/2017. Written informed consent was obtained from the next of the kin of the patient.

Patients aged 18–65 years with mild, moderate, or sTBI presenting for emergency surgery within 48 h of injury were included. Patients with extracranial injuries, patients with sTBI who were put on mechanical ventilation soon after admission from the emergency (because of concern of administration of sedation to manage mechanical ventilation), patients with preoperative hypotension, severe cardiac disease (known ischemic or severe valvular heart disease, myocardial infarction in the last 6 months, significant arrhythmias or heart failure), pulmonary disease (known chronic lung disease), liver disease (serum bilirubin >1.2 mg/dL), renal disease (serum creatinine >1.5 mg/dL), obesity, psychiatric illnesses, pregnant patients, those on chronic medications, and patients in whom BIS values could not be recorded were excluded from the study.[3] Patients were classified into mild, moderate, and sTBI based on the Glasgow Coma Scale (GCS) of 13–15, 9–12, and 3–8, respectively. Preoperative computed tomography (CT) of the brain was used to decide the injured and uninjured side or side with relatively minor injuries. In the operation theatre, electrocardiogram, noninvasive blood pressure (NIBP), and pulse oximeter (SpO_2) were attached, and the baseline values were noted. The patients were preloaded with 500 mL of Ringer lactate. A bilateral BIS sensor was attached to the patient's forehead, and baseline BIS values on the injured and uninjured sides were noted. Lignocaine (xylocard) 40 mg was administered intravenously before induction to reduce the pain of propofol injection. Anesthesia was induced with "a constant rate infusion of propofol" using a TCI pump. The patient's height (in meters), weight (in kg), age (in years), and gender were entered into the settings of the TCI pump, and the Schneider model was used. The patient's height was measured as recumbent height (RH) using a flexible tape, measured from the top of the head to the sole of the foot on a bed in a complete horizontal position.[4] Patients with TBI are often unconscious and unable to stand to be weighed accurately or to state their recent weight, so estimated actual body weight (ABW) was calculated using anthropometric measurements of the abdominal circumference (AC) measured at the level of the umbilicus (the smallest horizontal circumference in the area between the ribs and the iliac crest), and thigh circumference (TC) at 10 cm above the superior pole of the patella as described by Buckley *et al*.[5]

The formula used for calculating ABW:

Estimated ABW (in kg) = -47.8 + 0.78 * AC + 1.06 * TC (in males)

Estimated ABW (in kg) = -40.2 + 0.47 * AC + 1.30 * TC (in females)

*AC and TC measured in cm.

In our study, 20 patients could state their recent weight and for the rest, we used the above formula which has been validated

in patients of the emergency department by Buckley GR *et al*. To validate this formula in our population, we conducted a pilot study amongst 15 healthy volunteers and estimated their ABW using the above formula and also recorded their weight on a weighing scale. The difference between the calculated ABW and recorded weight was ±2.2 kg.

The maximum rate of propofol infusion in our study was limited to 250 mL/h. In order to have a continuous display of Cp and Ce of propofol, the TCI pump was set in the TCI mode with a high target Cp. During induction of anesthesia with propofol, recordings of Cp, Ce, and BIS score (from both hemispheres), NIBP, SpO_2, and heart rate (HR) were done every 30 s. A BIS value of 40 on the uninjured side was considered as the endpoint for induction and at this time point Cp, Ce, the total dose of propofol, and time taken for BIS to reach 40 were recorded from the TCI pump. The readings from the TCI pump were recorded by an anesthesia technician who was unaware of the grade of head injury. The rest of the anesthesia for the surgical procedure was continued as per the choice of the treating anesthesiologist. At the end of the surgery, after reversal of neuromuscular blockade, BIS values on the injured and uninjured side, and GCS were noted. In addition, GCS at discharge, length of hospital stay (LOHS), and GOSE at 30 days after the injury were retrieved (from the medical record or sometimes through a telephonic interview with the patient's kin). GOSE was graded from 1 to 8 (1- dead, 2- vegetative state, 3- severe disability lower, 4- severe disability upper, 5- moderate disability lower, 6- moderate disability upper, 7- good recovery lower, and 8- good recovery upper).

Statistical analysis

The sample size was calculated from a pilot study in 15 patients (5 patients each in mild, moderate, and sTBI group) for primary outcome parameter i.e., difference of Cp and Ce of propofol between the three groups. The effect size for Cp was found to be 0.33, and that for Ce was found to be 0.42. For achieving a power of 0.8 and assuming an alpha error of 0.05, the sample size for Cp was found to be 93 and for Ce, 60. Normally distributed quantitative variables were described as means and standard deviations, non-normally distributed quantitative variables as median and range, and qualitative variables as percentages. Normality was tested using the Shapiro–Wilk test. A one-way analysis of variance (ANOVA) was used to compare the age, weight, height, Cp, Ce, total dose of propofol, and time required for BIS to reach 40 between the groups with post-hoc pairwise comparisons conducted after correcting for multiple comparisons using Bonferroni test. Chi-square test/Fisher Exact test was used to test the difference of proportions of qualitative variables. Comparison of weight-adjusted dose of propofol for induction of anesthesia between males and females was done using independent sample t-test. Correlation between BIS and GOSE was done using the Spearman rank test. Within-group analysis of variables was done using Wilcoxon signed-rank test. Comparison of non-normally distributed variables between the groups was done using the Kruskal–Wallis test/Mann–Whitney *U* test. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Version 17.

Results

Of the 118 patients considered eligible, 96 patients were analyzed [Figure 1]. The demographics of the study population are presented in Table 1. Combined injuries (combination of extradural, subdural hematoma, or contusion) in contrast to an isolated hematoma was the most common diagnosis in all three groups. Midline shift on CT was more common in the sTBI group. Median baseline GCS was 14, 10, and 7 in mild, moderate, and sTBI groups, respectively, and the difference was statistically significant. There was no difference in the number of episodes of hypotension at induction between the groups.

Dose requirement of propofol

The Cp of propofol at induction of anesthesia was significantly less in patients with sTBI (9 ± 1.4 μg/mL) compared to patients with mild and moderate injury (9.9 ± 0.6 μg/mL and 10 ± 0.7 μg/mL). This difference was significant between patients with moderate and sTBI and between patients with mild and sTBI (P-value < 0.001), but not between mild and moderate TBI. Similarly, Ce of propofol was less in patients with sTBI group (4.48 ± 1.5 μg/mL) compared to mild TBI. This difference was significant between mild and severe head injury groups only, not between mild and moderate or between moderate and sTBI group (in mild- 6 ± 0.9 μg/mL, in moderate- 5.82 ± 0.98 μg/mL). The total dose of propofol required in sTBI group was 92.8 ± 29 mg, moderate TBI it was 127 ± 22 mg, and in the mild TBI group was 128 ± 18 mg. The requirement was significantly less in sTBI compared to mild TBI. However, when the requirement of propofol was adjusted for weight, the difference became significant between the moderate and severe head injury group and between mild and severe head injury groups ($P < 0.001$). The time to induction was significantly less in patients with sTBI compared to mild and moderate TBI. [Figure 2 and Table 2]

Comparison of BIS values between the three groups

Table 3 shows the values of BIS at baseline (before induction of anesthesia) and the end of surgery on the normal and injured side in the three groups. The baseline BIS were in the normal hemisphere were significantly higher than those in the injured hemisphere within each group (the difference of 8.8-10 score). The BIS values were highest in the mild TBI group and lowest

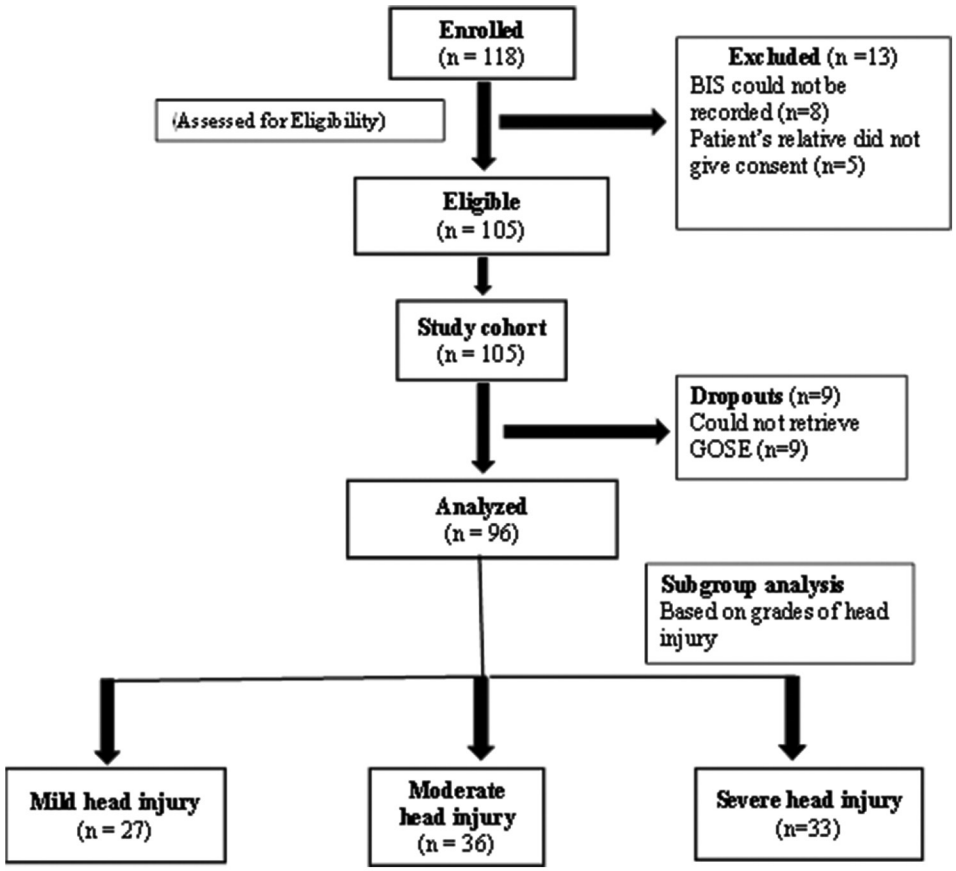

Figure 1: Flow diagram of the number of patients at each step in the study protocol

Table 1: Comparison of demographic variables in the three groups

Variable	Mild TBI *n*=27	Moderate TBI *n*=36	Severe TBI *n*=33	*P*
Age (years)	35.48±13.6	40.03±12.8	42.64±14.0	0.13
Height (m)	1.66±0.08	1.64±0.08	1.62±0.08	0.14
Weight (kg)	67.93±9.9	70.92±11.7	67.64±10.9	0.40
Male: Female (numbers)	22:5	30:6	27:6	0.97
No. of patients with combined injuries (%)	11 (40.7)	20 (55.6)	13 (39.4)	0.017*
No. of patients with midline shift >5 mm (present : absent)	12:15	25:11	27:6	0.001*
Baseline GCS	14 (1415)	10 (9.25-12)	7 (5-8)	<0.001*

*GCS- Glasgow Coma Scale TBI – traumatic brain injury Age, weight and height – mean±SD, baseline GCS- median (interquartile range), * P value is significant*

in sTBI group. The BIS values were statistically different between groups (on the normal side - 89, 81, and 65.4 in mild, moderate, and sTBI and on the injured side- 80.4, 71.2, and 55.3 in mild, moderate, and sTBI, respectively).

Similarly, at the end of the surgery, the BIS values on the normal side were significantly higher than those on the injured side within each group ($P < 0.001$) and were highest in mild TBI and lowest in sTBI group ($P < 0.001$). The BIS values were statistically different between groups (on the normal side –84.4, 78.2, and 64.8 in mild, moderate, and sTBI as well as on the injured side –76, 68.9, and 54.4 in mild, moderate, and sTBI). The difference of BIS score between normal and injured sides did not change after surgery in any of the groups as well as in sTBI group on the injured side i.e., presurgery interhemispheric difference (in BIS values) did not differ from that after surgery (in mild TBI, interhemispheric difference of 8.78 at baseline vs 8.44 postsurgery, moderate TBI group - 9.83 vs 9.28 and in sTBI - 10.12 vs 10.4, P value = 0.977, 0.493 and 0.895, respectively). Propofol requirement was high in females (2.1 ± 0.58 mg/kg) compared to males (1.63 ± 0.42) ($P < 0.001$). GCS at discharge was 15, 13, and 10, and LOHS was 1.67 ± 0.961, 4.2 ± 4.87, and 8.21 ± 8.5 days in the mild, moderate, and sTBI groups, respectively. GOSE was 8 (8–8), 7 (7–8), and 6 (6–7) in the mild, moderate, and sTBI group, respectively. There

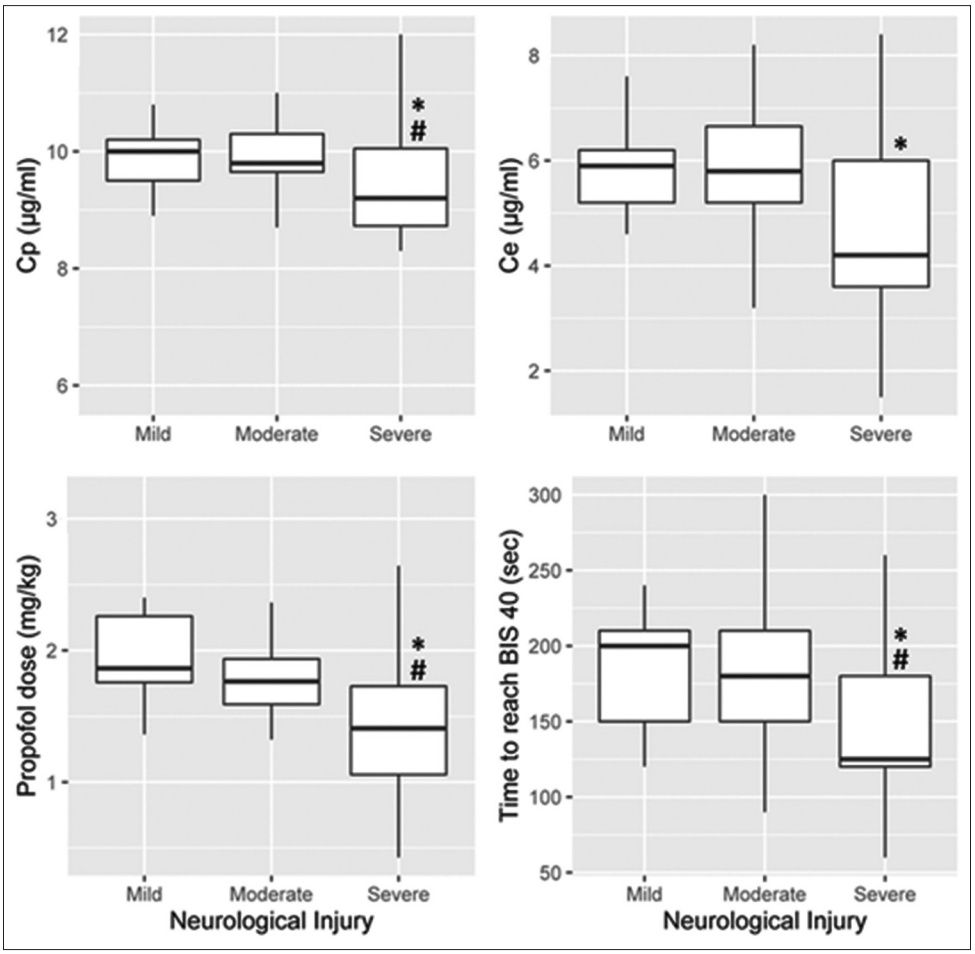

Figure 2: Boxplots of variables grouped by neurological injury severity. *- statistically significant compared to mild, #- compared to moderate. $P < 0.05$ for statistical significance. The box consists of the median (middle hinge), first quartile (lower hinge), and third quartile (upper hinge). The upper whisker extends from the hinge to the largest value ≤1.5 *IQR from the hinge (where IQR is the interquartile range). The lower whisker extends from the hinge to the smallest value ≤1.5 * IQR of the hinge

Table 2: Plasma concentration (Cp), effect-site concentration (Ce), the dose of propofol, and time to induction of anesthesia in the three groups

Variable	Mild (*n*=27)	Moderate (*n*=36)	Severe (*n*=33)	*P*
Cp ((µg/mL)	9.9±0.6	10±0.7	9±1.4	<0.001*
Ce (µg/mL)	6±0.9	5.82±0.98	4.48±1.5	<0.001*
The total dose of propofol (mg)	128±18	127±22	92.84±29	<0.001*
Weight adjusted propofol dose (mg/kg)	1.92±0.29	1.84±0.45	1.41±0.5	<0.001*
Time required for BIS to reach 40 (s)	185.56±33.4	176.39±42.43	140±44	<0.001*

*Cp - plasma concentration, Ce – effect-site concentration, BIS- Bispectral index Cp and Ce are expressed as µg/mL. Data values are in mean±standard deviation. *P-value is significant*

was a strong positive correlation between baseline BIS and GOSE (r = 0.63 on the normal side, 0.89 on the injured side, $P < 0.001$). There was also a weak positive correlation between BIS at the end of surgery and GOSE (r = 0.54 on the normal side and 0.59 on the injured side, $P < 0.001$).

Discussion

Our study demonstrated that the dose of propofol required for induction of anesthesia as evaluated by Cp and Ce was significantly less in patients with sTBI compared to mild TBI. In patients undergoing surgery for large brain tumors (>30 mm) with midline shift, the dose of propofol required to abolish response to verbal command and the tetanic stimulus was 23% and 32% less, respectively, compared to patients with small tumors and also in non-neurosurgical healthy patients.[2] The authors induced anesthesia using the fixed predetermined dose of propofol injected as a bolus. Quantal dose-response curves of propofol for suppressing response to verbal command and tetanic stimulus were compared. We tried to improve upon the methodology by using continuous infusion of propofol using the TCI pump (Schneider model shown to be better

Table 3: Baseline and end of surgery BIS on normal and injured side in the 3 groups

	Mild	Moderate	Severe
Baseline BIS			
Normal side	89.19±5.5	81.06±8.4	65.42±12
Injured side	80.4±7.8	71.2±9.4	55.3±11.6
P	<0.001*	<0.001*	<0.001*
BIS at the end of surgery			
Normal side	84.4±6.3	78.2±7.6	64.82±11.7
Injured side	76±7.7	68.92±7.8	54.42±10.7
P	<0.001*	<0.001*	<0.001*

*BIS- Bispectral index Data values are presented as are mean±SD. *P-value is statistically significant*

in neurosurgical patients) and an objective parameter of BIS of 40 to determine the endpoint of induction.[6] The decreased requirement of propofol in patients with sTBI can be attributed to multiple factors. First, TBI can lead to widespread biochemical changes in the brain including an alteration in the gamma-aminobutyric acid (GABA) and N-methyl-D-aspartic acid (NMDA) receptors which mediate the action of anesthetics. Second, a breach in the blood-brain barrier may increase the permeability of drugs, increasing the Ce of anesthetics, thereby, reducing the time and dose of a drug required for induction. Third, animal studies have shown that after superficial cortical injury, there is cerebral hypometabolism in the form of decreased glucose utilization. This effect can be seen as early as 4 h after injury, and the maximum effect is at 3 days. This cortical hypometabolism is a reflection of functional depression and most likely involves activation of serotonergic and noradrenergic systems. The requirement of propofol in the brain tissue which is depressed and hypometabolic is unpredictable and might be reduced.[7] The above changes would be proportionately more in patients with sTBI compared to mild and moderate TBI. The hematoma and/or parenchymal tissue edema leads to an increase in intracranial pressure (ICP), and the resulting cerebral ischemia causes slowing of EEG and a decrease in baseline BIS values.[8,9] Increased ICP can also lead to sudden pressure on the brain stem or displacement of the reticular activating system leading to a decrease in the level of consciousness. An increase in ICP is much more in patients with a moderate and severe head injury when compared to mild head injury. All these factors may be responsible for a reduction in the requirement of propofol at an induction in patients with a severe grade of TBI compared to a mild one. In our patients, ICP was not measured. The pharmacokinetics of propofol is not different in neurosurgical patients when compared to healthy volunteers.[10,11] The pharmacokinetics can be altered by age, sex, weight, pre-existing disease, and concomitant medications.[12,13] In our study, there was no difference in age or gender distribution between the groups. Patients with severe comorbidities were excluded from the study. The patients in all three groups received mannitol and phenytoin preoperatively. Hence, it is unlikely that altered pharmacokinetics of propofol is responsible for observed differences in propofol requirement among the study groups. Baseline BIS (before propofol infusion) on injured and noninjured sides were significantly different between the three groups and within each group. Ebthehaj *et al.*[14] also observed a significant correlation between GCS and BIS in patients with TBI ($r = 0.88$, $P < 0.05$). We also observed that with increasing severity of TBI, the BIS value decreases significantly. BIS has also been found to have an inverse association with ICP and a direct association with CPP.[15] Our study had similar findings probably due to a similar mechanism.

During cerebral ischemia, there is progressive slowing of EEG, decrease in high-frequency activity, and eventually isoelectric EEG.[16] Previous literature supports the finding of a reduction in BIS during cerebral hypoperfusion.[17,18] Changes in BIS value with cerebral ischemia lack specificity because several other factors such as reduced mean arterial pressure (MAP) can alter BIS. However, in our study, there was no difference in MAP at induction between the three groups. Patients who were hypotensive at presentation to the emergency department were also excluded from our study.

The difference in BIS values between the normal (or less injured) and the injured side was significant within each group, which is not seen in a healthy patient. EEGs from the two sides can differ because of underlying disease pathology or anatomical differences. Lee *et al.*[19] reported two cases of unilateral severe carotid artery stenosis, where BIS values decreased more on the diseased side when MAP decreased below 70 mmHg.

The interhemispheric difference of BIS value did not change after the surgery. We would expect that surgery would reduce the ICP, leading to improvement in BIS on the injured side, and therefore interhemispheric BIS disparity should decrease or BIS would increase on both sides of the brain, leaving the interhemispheric disparity unaffected. However, none of the BIS values increased after surgery. The unaltered BIS numbers at the end of surgery were because we noted the BIS numbers immediately after administering reversing relaxant. Probably, at this time, residual effects of anesthetics were persisting or it may be because of any intraoperative brain insult. We did not record BIS values at discharge which could have given us a better insight into the beneficial effect of surgery on BIS values. We found a positive correlation between GOSE and BIS (both at baseline and the end of surgery). Mahadewa *et al.*[20] demonstrated a strong correlation between GOSE score and BIS value in patients of TBI. The authors indicated that BIS scores at admission

may be useful to predict the outcomes in patients with TBI. The dose of propofol required for induction was different between females and males in our study. The difference in drug sensitivity (low drug sensitivity in males) and in the pharmacokinetics of propofol (larger volume of distribution and faster rate of clearance in females when compared to males) have been shown to be responsible for the observed difference in emergence times between males and females.[21]

There are limitations to our study. First, considering the fact that we could not measure the weight of the patients, we estimated their ABW using the formula by Buckley *et al*. There was a difference of ±2.2 kg between estimated and recorded weight, which could alter dose requirement. Second, postoperative BIS was recorded in the immediate postoperative period. BIS value at a later time point (maybe at 24 h), and its difference from baseline BIS could have provided useful information. Similarly, GCS was noted in the operation theatre immediately after the surgery which might provide wrong information owing to residual effects of anesthetics at this time point. Third, an inherent lag period of 10 to 15 s in the BIS algorithm could have led to more drug delivery than required. But at the infusion rate of 250 mL/h, the amount of propofol that would have got infused over 10–15 s would be minimal. Lastly, we did not monitor ICP in our patients. This study is likely to have practical implications in clinical practice, and it is advisable to administer lower doses of propofol to patients with sTBI. This can help in preventing hypotension which is a known secondary injury in patients with TBI.

Conclusions

The requirement of propofol for induction of anesthesia is significantly reduced in patients with sTBI compared to those with milder injury. Female patients require a higher dose of propofol than males. Bilateral BIS is a novel, noninvasive monitor which can be used to assess the endpoint of induction, the severity of the injury, quantify interhemispheric differences in EEG, and in predicting neurological outcomes following TBI.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Kamal VK, Agrawal D, Pandey RM. Epidemiology, clinical characteristics and outcomes of traumatic brain injury: Evidences from integrated level 1 trauma center in India. J Neurosci Rural Pract 2016;7:515-5.
2. Chan MTV, Gin T, Poon WS. Propofol requirement is decreased in patients with large supratentorial brain tumor. Anesthesiology 1999;90:1571-6.
3. Wang C, Su Q, Zhang SW, Yin CH, Wang H, Wang BE. A clinical study on the diagnostic criteria of multiple organ dysfunction syndrome. Zhonghua Wai Ke Za Zhi 2009;47:40-3.
4. Gray DS, Crider JB, Kelley C, Dickinson LC. Accuracy of recumbent height measurement. JPEN J Parenter Enteral Nutr 1985;9:712-5.
5. Buckley RG, Stehman CR, Dos Santos FL, Riffenburgh RH, Swenson A, Mjos N, *et al*. Bedside method to estimate actual body weight in the emergency department. J Emerg Med 2012;42:100-4.
6. Sahinovic MM, Eleveld DJ, Miyabe-Nishiwaki T. Pharmacokinetics and pharmacodynamics of propofol: Changes in patients with frontal brain tumours. Br J Anaesth 2017;118:901-9.
7. Pappius HM. Cortical hypometabolism in injured brain: New correlations with the noradrenergic and serotonergic systems and with behavioral deficits. Neurochem Res 1995;20:1311-21.
8. Mokri B. The Monro-Kellie hypothesis: Applications in CSF volume depletion. Neurology 2001;56:1746–8.
9. Merat S, Levecque JP, Le Gulluche Y, Diraison Y, Brinquin L, Hoffmann JJ. BIS monitoring may allow the detection of severe cerebral ischemia. Can J Anesth 2001;48:1066–9.
10. Lim TA, Gin T, Tam YH, Aun CS, Short TG. Computer-controlled infusion of propofol for long neurosurgical procedures. J Neurosurg Anesthesiol 1997;9:242–9.
11. Hans P, Coussaert E, Cantraine F, Pieron F, Dewandre PY, d'Hollander A, *et al*. Predictive accuracy of continuous propofol infusions in neurosurgical procedures: Comparison of pharmacokinetic models. J Neurosurg Anesthesiol 1997;9:112–7.
12. Kay NH, Sear JW, Uppington J. Disposition of propofol in patients undergoing surgery. A comparison in men and women. Br J Anesth 1986;58:1075–9.
13. Kirkpatrick T, Cockshott ID, Douglas EJ. Pharmacokinetics of propofol (diprivan) in elderly patients. Br J Anesth 1988;60:146–50.
14. Ebtehaj M, Yaqubi S, Seddighi AS, Seddighi A, Yazdi Z. Correlation between BIS and GCS in patients suffering from head injury. Ir J Med Sci 2012;181:77–80.
15. Dunham CM, Ransom KJ, McAuley CE, Gruber BS, Mangalat D, Flowers LL. Severe brain injury ICU outcomes are associated with cranial-arterial pressure index and noninvasive bispectral index and transcranial oxygen saturation: A prospective, preliminary study. Crit Care 2006;10:R159. doi: 10.1186/cc5097.
16. Clute HL, Levy WJ. Electroencephalographic changes during brief cardiac arrest in humans. Anesthesiology 1990;73:821–5.
17. Mourisse J, Booij L. Bispectral index detects period of cerebral hypoperfusion during cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2003;17:76–8.
18. Hashimoto H, Nakamura H, Hirota K. Marked reduction in bispectral index with severe bradycardia without hypotension in a diabetic patient undergoing ophthalmic surgery. J Anesth 2008;22:300–3.
19. Lee EH, Choic IC, Song JG, Jeong YB, Hahm KD, Son HJ. Different bispectral index values from both sides of the forehead in unilateral carotid artery stenosis. Acta Anaesth Scand 2009;53:134–6.
20. Mahadewa TGB, Senapathi TGA, Wiryana M, Aribawa IGNM, Arparitna KY, Ryalino C. Extended Glasgow outcome scale correlates with bispectral index in traumatic brain injury patients who underwent craniotomy. Open Access Emerg Med 2018;10:71–4.
21. Hoymark SC, Raeder J. Why do women wake up faster than men from propofol anaesthesia? Br J Anaesth 2005;95:627-33.