Original Article

To ascertain the plasma concentration of propofol to achieve bispectral index-guided sedation using a target-controlled infusion in patients undergoing elective surgeries under neuraxial anaesthesia

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Submitted: 17-Dec-2021
Revised: 13-Sep-2022
Accepted: 05-Dec-2022
Published: 20-Dec-2022

Access this article online

Website: www.ijaweb.org

DOI: 10.4103/ija.ija_1076_21

Quick response code

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ABSTRACT

Background and Aims: Sedation improves patient satisfaction, comfort and acceptance of regional anaesthesia. Propofol using bispectral index (BIS)/target-controlled infusion (TCI) system can be an optimal method of sedation, as it combines objective measurement of sedation using BIS along with maintenance of a steady plasma concentration of propofol with the TCI device. The aim of this study was to ascertain the dose and safety of propofol using BIS/TCI system for sedation in patients undergoing surgeries under neuraxial anaesthesia. **Methods:** One hundred and seven adult patients, undergoing elective surgical procedures under spinal or combined spinal epidural anaesthesia, were recruited. Propofol infusion was started with TCI at an initial target plasma concentration (Cpt) of 1.2 μg/mL, and after equilibration between Cpt and effect site concentration (Ce), propofol was then adjusted in increments and/or decrements of 0.2 μg/mL in order to maintain a BIS value between 60 and 80. The average time to reach BIS = 80 after starting infusion was 7.32 ± 3.13 minutes. The objective was to calculate mean Cpt value maintaining BIS between 60 and 80 and to observe recovery time and complications. **Results:** Mean Cpt value was 1.13 ± 0.17 μg/mL with 95% confidence interval (1.10–1.16 μg/mL). In 85% of patients, a BIS value of 60–80 was maintained at Cpt ≤ 1.2 μg/mL. No patient had severe complications requiring stoppage of infusion. **Conclusion:** Propofol sedation using BIS/TCI system can provide safe and convenient sedation during neuraxial anaesthesia at very low plasma concentration, Cpt ≤ 1.2 μg/mL in majority of patients. There were no periprocedural complications, and recovery was rapid.

Key words: Bispectral index, propofol sedation, regional anaesthesia, target controlled infusion (TCI)

INTRODUCTION

Spinal anaesthesia is a commonly used technique for lower limb and lower abdominal surgeries. One of the major drawbacks is patients' anxiety, leading to decreased satisfaction and acceptance of this technique. Thus, sedation is an integral part of regional anaesthetic technique. Maintaining an adequate level of sedation is equally important, as deeper levels are commonly associated with adverse cardiovascular and respiratory events. Therefore, patients should

How to cite this article: Chhabra D, Bhatia P, Sethi P, Kaloria N, Kumar M, Kaur M. To ascertain the plasma concentration of propofol to achieve bispectral index-guided sedation using a target-controlled infusion in patients undergoing elective surgeries under neuraxial anaesthesia. Indian J Anaesth 2022;66:832-6.

preferably be lightly or moderately sedated, which can be challenging for the anaesthesiologist.

Various agents are available for sedation such as benzodiazepines, ketamine, clonidine, dexmedetomidine, propofol, opioids with their own benefits and disadvantages. Propofol seems to be an attractive option as it has a favourable pharmacokinetic profile, with a rapid onset of action and early recovery with easy titration of level of sedation.[1] Single or repeated boluses of propofol for sedation have a rapid onset but lead to unstable plasma levels with the consequent adverse effects like respiratory and haemodynamic instability at peak concentrations and inadequate level of sedation at trough plasma levels. Continuous infusion using manual infusion pump following a bolus injection often leads to increasing blood concentration of propofol over time, requiring repeated adjustments to maintain adequate level of sedation. This can be troublesome, especially during prolonged surgeries. The problem of repeated dose adjustments with manual infusion pumps is overcome by pharmacokinetic models for propofol used in target-controlled infusion (TCI) systems. The anaesthesiologist sets a target propofol concentration, and the infusion rate is adjusted automatically.

Bispectral index (BIS) measures the level of consciousness objectively and noninvasively. With BIS, the operator can adjust sedative dose more confidently by monitoring the level of sedation objectively, without interobserver variation.

Many studies have described the efficacy and safety of propofol TCI for sedation in endoscopic procedures, but there is little data about the use and safety of propofol BIS/TCI system for sedation during spinal anaesthesia.[2] This study was planned to find the average value of target plasma concentration (Cpt) for sedation using the Marsh model TCI maintaining BIS between 60 and 80 during neuraxial anaesthesia. We also observed time to achieve BIS value of less than 80, any complications and recovery time after stopping the infusion and its correlation with age, gender and the average dose of propofol consumed.

METHODS

This prospective single arm interventional study was conducted from January 2019 to December 2020, at a tertiary healthcare institute after approval from the institute's ethics committee (AIIMS/IEC/2018/1573 dated 24 December 2018) and registration with the Clinical Trials Registry of India (CTRI/2019/02/017641), in accordance with the principles of the Declaration of Helsinki. After taking written informed consent, 107 patients, of American Society of Anesthesiologists physical status I and II, aged between 18 and 70 years, scheduled for surgery with an expected duration of one to three hours under spinal or combined spinal epidural anaesthesia, were included. Patients who refused to give consent, who had neurologic, psychiatric or hepatic disorders and pregnant females were excluded.

In the operating room, all routine standard monitoring along with BIS electrodes (BIS_ monitor, Covidien Medical, Boulder, Colorado, USA) was attached. Spinal anaesthesia was given using 0.5% hyperbaric bupivacaine. End tidal capnography monitor was attached along with face mask.

After confirmation of block success, continuous intravenous infusion of propofol was started using a TCI system (B. Braun Perfusor® Space target controlled infusion, Melsungen, Germany). In this study, Marsh pharmacokinetic model was used, as it had shown better correlation with both Observer's Assessment of Alertness/Sedation (OAA/S) and BIS scores during propofol sedation,[3] and the propofol infusion was started at a Cpt of 1.2 μg/ml, based upon recommendations of a previous study.[4] Initial BIS value was recorded two minutes after predicted effect site concentration (Ce) was equal to Cpt to allow equilibrium between effect site (central nervous system) and central compartment.[3] The time taken to achieve BIS less than 80 was noted. The sedation level was noted using the responsiveness component of OAA/S score simultaneously with BIS scores. The target BIS ranged between 60 and 80. If the BIS value was less than 60 or more than 80, then the Cpt was decreased or increased by 0.2 μg/ml, respectively, and corresponding BIS value and OAA/S score were noted after equilibrium between Ce and Cpt was achieved. If the BIS value came in the range of 60–80, the infusion was continued at that Cpt value, and BIS values were recorded every 5 minutes. If BIS value lay outside 60–80 range, Cpt was decreased or increased further by 0.2 μg/ml, and BIS value reassessed until it was between 60 and 80. At the completion of surgery, infusion was stopped, and the duration of infusion and recovery time were noted. Recovery time was defined as time to reach OAA/S score 5 after stopping the infusion. The case was excluded from the analysis if the procedure

was converted to general anaesthesia or abandoned due to any reason after giving spinal anaesthesia. Intraoperative complications were recorded and managed appropriately.

The sample size was calculated using the study by Imagawa A and colleagues, wherein they found that 80% of patients achieved BIS 60–80 with propofol infusion by TCI at a plasma concentration of less than 1.6 μg/ml,[4] and suggested 1.2 μg/ml as an ideal default starting Cpt setting. We calculated a sample size of 107 (95% CI, 10% relative error and 10% contingency). Data was entered in Microsoft Excel and analysed using Statistical Package for Social Sciences for Windows (version 23, SPSS, Chicago, Illinois, USA). Nominal data was described using counts and percentages, ordinal data like sedation score was described using median [interquartile range], and continuous data was described using mean ± standard deviation. Spearman's coefficient was calculated to test the correlation between BIS and OAA/S and that between recovery time with age, duration of infusion and average dose of propofol used. A $P < 0.05$ was considered statistically significant.

RESULTS

A total of 160 patients came for elective surgeries during the study period, out of which 111 were recruited after applying the exclusion criterion, of which 4 patients were converted to general anaesthesia. Therefore, a total of 107 patients were analysed [Table 1]. Of these 107 patients, 52.34% (number (n) = 56) underwent orthopaedic surgery, 28.97% (n = 31) underwent gynaecological procedures, 10.28% (n = 11) had general surgery, 5.61% (n = 6) had plastic surgery, 1.87% (n = 2) had urological procedures and 0.93% (n = 1) had oncologic surgery.

The mean duration of propofol infusion was 84.45 ± 18.62 minutes, ranging from 60 to 150 minutes. However, the data was analysed only till 60 minutes, as there were smaller number of patients having infusions beyond this time to have a statistically significant result. In 85% of patients, we were able to maintain a BIS value of 60–80 at Cpt of ≤1.2 μg/mL. The mean value of target propofol concentration was 1.13 ± 0.17 μg/mL (95% CI 1.10–1.16 μg/mL). The mean propofol consumption was 3.05 ± 0.37 mg/kg/hour. Median BIS value was 71 (66–74), while median of OAA/S score was 3 (2–3). The time taken to reach BIS of 80 after starting the infusion varied from 2 to 20 minutes with a mean of 7.32 ± 3.13 minutes. The recovery time ranged from 0 to 15 minutes with a mean of 7.39 ± 3.41 minutes. We did not find any correlation of recovery time with age, duration of infusion of propofol and average dose of propofol used. There was a significant positive correlation between the BIS value and OAA/S (Spearman's rho = 0.397, $P < 0.001$), i.e., as OAA/S scores increase, BIS value also increases. No patient had a severe side effect requiring stoppage of infusion [Table 2].

DISCUSSION

There is no single agent or method that can be considered ideal for sedation in all patients undergoing regional anaesthesia. However, propofol BIS/TCI system can be one of the available options for this purpose. Based upon recommendations of Imagawa A and colleagues for sedation during endoscopic procedures, initial target plasma propofol concentration of 1.2 μg/mL was chosen.[4] We were able to maintain a BIS value of 60–80 in 85% of our patients at or below 1.2 μg/mL Cpt of propofol. The mean Cpt value was 1.13 ± 0.17 μg/mL (95% CI 1.10–1.16 μg/mL) for maintaining a stable sedation (BIS value ranging from 60 to 80). These values are lower than that of the previous study possibly due to higher level of stimulation during upper gastrointestinal endoscopies, compared to complete anaesthesia of the operating part during neuraxial anaesthesia in our study.[4] Another postulate can be that cerebral

Table 1: Demographic variables and clinical parameter

Sociodemographic parameters	Values (*n*=107)
Age (years) (mean±SD)	41.39±15.21
Gender (male/female)	45/62
Weight (kg) (mean±SD)	67.53±10.46
ASA grade (I/II)	76/31

SD: Standard deviation, ASA: American Society of Anesthesiologists. All data are represented as n=number of patients except age and weight which are expressed as mean±SD

Table 2: Side effects

Side effects	*n*=Number of patients*	Incidence (%)
Hypotension (Fall of MAP ≥30% from baseline and/or SBP <90 mmHg)	23	21.5
Hypoxia (SpO_2 <90%)	1	0.93
Bradycardia (HR <50/min)	2	1.87
Pain on infusion	8	7.48
Excessive talking	5	4.67
Hypotension + hypoxia	2	1.87

SBP: Systolic blood pressure, SpO_2: Peripheral oxygen saturation, HR: Heart rate, MAP: Mean arterial pressure. Data depicted as n=number of patients*. Incidence is percentage (%) of the patients having side effects

deafferentation during spinal anaesthesia in our study population reduced the sedative requirements.[5] Even though the exact mechanism is still debatable, spinal anaesthesia blocks active muscle movements which stimulates the reticular activating system, mediated in part by muscle afferent receptors. Cerebral deafferentation could also explain the lower Cpt in our study compared to Cpt values of 1.3 ± 0.33 μg/mL (CI 1.2–1.4) and 1.7 ± 0.39 μg/mL (CI 1.6–1.8) to achieve an OAA/S sedation score of 4 and 3, respectively, in a previous study of patients undergoing lower limb orthopaedic surgery under combined sciatic-femoral nerve block.[6]

From this study, we cannot opine on actual blood concentrations of propofol as we relied upon its predicted concentrations from Marsh model. In day-to-day clinical practice, it is obviously not feasible to measure the actual blood levels of propofol to titrate sedation. However, our findings are similar to those of Skipsey IG and colleagues, who found the mean measured blood propofol concentration of 1.05 μg/mL to correspond to a similar level of sedation.[7]

The average propofol consumption in our study was 50.75 ± 6.15 μg/kg/min. We cannot extrapolate this rate for propofol infusion to a manual infusion pump for sedation. This is because the rate of infusion is not constant using TCI pump as it infuses at a higher rate initially to achieve a set plasma concentration, and later, the rate reduces to maintain a steady state. Interestingly, our finding is similar to the study by Ghimire A and colleagues where propofol infusion at the rate of 50 μg/kg/min provided optimal sedation in patients undergoing surgeries under spinal anaesthesia.[8] This may suggest that propofol consumption is similar using TCI and manual infusion pump. However, this needs further validation.

Hypotension occurred in 23 patients (21.5%), mainly within the first 20 minutes of starting the infusion. This can be explained by the synergistic effect of spinal anaesthesia and propofol.[9] Hypotension was easily managed with fluid bolus and phenylephrine. Only three out of 107 patients had a desaturation episode. Slower onset of sedation with BIS/TCI system (BIS value of 80 being achieved in 13.4 minutes in 95% of patients after starting the infusion) along with use of oxygen supplementation with capnographic monitoring might account for the low incidence of hypoxaemia. None of the patients required airway intervention or assisted ventilation. Eight patients complained of pain on infusion. This is a known side effect as propofol causes venous irritation. This can be offset by giving lignocaine, avoiding veins on the dorsum of the hand, using a larger vein and pretreatment with opioids. In five patients, we observed excessive talking. This paradoxical excitement can be seen with sedatives and anaesthetic drugs like benzodiazepines and propofol. These responses vary from increased talkativeness, disorientation, excessive movement, agitation and loss of cooperation. The mechanism is still unclear but is proposed to have a similar mechanism of action as alcohol, activating γ-aminobutyric acid-A receptors.[10]

After stopping the infusion, 50% of patients achieved an OAA/S score of 5 at 7 minutes, and 95% of the patients achieved OAA/S score of 5 at 14 minutes. We did not find any correlation of recovery time with age, duration of infusion and average dose of propofol consumed [Table 3]. Shorter recovery time enables effective utilisation of operating room resources and higher patient satisfaction.

This study highlights the fact that lower doses of propofol can be used for sedation under regional anaesthesia especially with TCI. We recommend initiating sedation with lower doses of propofol (Cpt <1.2 μg/mL), as we were able to achieve adequate sedation in almost 85% patients with Cpt ≤1.2 μg/mL.

There are two limitations to our study. First, the data was evaluated up to 60 minutes only. Therefore, we cannot extrapolate our study results for infusion duration more than this time, as the context-sensitive half-life of propofol increases with increasing duration of infusion. Second, our study population mainly consisted of young and middle-aged people. Propofol dose requirements reduce with increasing age. Hence, elderly population might require a lesser dose.

Table 3: Correlation between recovery time and age, duration of infusion and average dose of propofol used

Variable	Compared with	Correlation coefficient	*P*
Recovery time (minutes)	Recovery time (minutes)	1.000	
Recovery time (minutes)	Age	0.174	0.73
Recovery time (minutes)	Duration of infusion (minutes)	0.015	0.878
Recovery time (minutes)	Average dose of propofol (μg/kg/min)	0.005	0.960

This table depicts correlation between different parameters, and $P<0.05$

CONCLUSION

BIS-guided TCI infusion may help in providing sedation even at very low plasma concentration of propofol (Cpt of <1.2 μg/mL) for regional anaesthesia. This study proves that usage of BIS-guided propofol infusion can be a safer alternative for sedation under regional anaesthesia.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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