A randomized trial of propofol consumption and recovery profile with BIS-guided anesthesia compared to standard practice in children

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Summary

Aim: To evaluate the impact of bispectral index (BIS) monitoring on the consumption of propofol and recovery from anesthesia compared to the standard clinical practice in children.

Background: Titrating propofol administration using BIS reduces its requirement and shortens the recovery from anesthesia in adults. However, there is still mixed evidence for utility of anesthesia depth monitors in reducing anesthesia requirement in children.

Methods/Materials: A prospective randomized study was conducted in 50 ASA I children of 2–12 years, randomly assigned into standard practice (SP) or BIS group. After induction with propofol, anesthesia was maintained with 150 μg·kg⁻¹·min⁻¹ propofol infusion. The propofol infusion rate was altered by 20 μg·kg⁻¹·min⁻¹ to maintain the systolic blood pressure within 20% of the baseline (SP group) or BIS value between 45 and 60 (BIS group). The rate of propofol infusion was reduced by 50% about 15 min before the end of surgery. The amount of propofol used and the times from stopping the propofol infusion to eye opening, extubation, response to commands and attaining Steward score of 6 were recorded.

Results: There was no evidence of a difference in the mean propofol consumption in the two groups (BIS 232.6 ± 136.7 mg, SP 250.8 ± 118.2 mg). The intraoperative hemodynamics and BIS values were similar in the two groups. There was no evidence for a difference between groups in the mean times from termination of anesthetic to eye opening, extubation, response to commands and to achieve a Steward Recovery score of 6.

Conclusions: Our study showed no benefit of BIS-guided propofol administration on anesthetic consumption or recovery compared to standard anesthetic practice.
Introduction

The bispectral index (BIS), a variable derived from the electroencephalograph (EEG), is reported to have the ability to measure the hypnotic component of the anesthetic state (1,2). EEG-derived variables have been claimed to have the advantage of reducing drug consumption, minimizing the chance of awareness, and shorten the period of emergence and recovery from anesthesia (3–6). Many studies have evaluated the relationship between BIS and sedation, consciousness and anesthetic concentration, and it has been established that anesthetic titration using BIS monitoring reduces anesthetic requirement and shortens recovery in adult surgical patients (6,7).

In the pediatric population, the ability of BIS to accurately follow variations in anesthetic agent concentration and evaluate depth of anesthesia remains controversial. BIS-guided titration of inhalational agents such as sevoflurane, has been found to decrease anesthetic use and shorten recovery in older children (4). Propofol is an anesthetic agent that is now being used for sedation and general anesthesia in children (8–10). Few studies in children have evaluated BIS under total intravenous anesthesia (TIVA) with propofol (9,11–13). Weber et al. (12) reported reduced propofol consumption and faster emergence in children during TIVA with propofol/remifentanil using auditory evoked potential (AEP). However, there is no study to show whether titration of propofol using BIS monitoring reduces anesthetic requirement and shortens recovery in pediatric population. The primary aim of the present study was to evaluate the impact of BIS monitoring on the consumption of propofol. Assessment of recovery from anesthesia compared to the standard clinical practice in children was the secondary aim of the study.

Materials and methods

A prospective, randomized controlled study was conducted in 50 ASA I children in the age group of 2–12 years undergoing elective urogenital surgery of about 1 h duration under general anesthesia. Children were enrolled into the study after Institute Ethics Committee approval and informed parental consent. Patients with epilepsy and those taking drugs known to affect EEG were excluded from the study. The children were randomly assigned by a computer-generated randomization table into standard practice (SP) group or BIS group. Randomization to the two groups was performed by opening a sealed envelope. Children fasted 6 h for solids and 4 h for fluids and were premedicated with 0.5 mg·kg⁻¹ of midazolam orally, about 30 min before the start of anesthesia. An intravenous cannula was introduced after EMLA cream (eutectic mixture of 2.5% lidocaine and 2.5% prilocaine, Prilox; Neon Laboratories, Mumbai, India) had been applied at the site of venipuncture for at least an hour. The patients were then transferred to the operation theater. Baseline recording of heart rate (HR), NIBP and BIS was performed just before the start of the induction of anesthesia. The intraoperative monitoring consisted of ECG, NIBP, pulse oximetry, endtidal carbon dioxide (Aestiva/5; Datex-Ohmeda Inc., Madison, WI, USA) and BIS at every 5 min interval. BIS was measured using BIS Monitor Model A-2000 IP X 2 (Aspect Medical Systems Inc., Newton, MA, USA) and commercially available disposable BIS sensor strips. The strip has three electrodes and is placed on the forehead so that the proximal electrode is over the nasion, and the distal electrode is midway between the tragus and the outer canthus of the eye. The skin was prepared with alcohol at BIS site to maintain impedances at <10 kΩ.

Anesthesia was induced with 3 mg·kg⁻¹ of propofol and morphine 0.1 mg·kg⁻¹. Atracurium (0.5 mg·kg⁻¹) was used to facilitate tracheal intubation. Subsequently, anesthesia was maintained with nitrous oxide in oxygen (FiO₂ 0.33) and propofol infusion at an initial rate of 150 μg·kg⁻¹·min⁻¹. Intraoperatively fluid administration was with N/2 saline–dextrose solution, followed by normal saline based on the formula of Holliday and Segar (14). The anesthetist conducting the anesthesia in the SP group was masked to the BIS values. In this group, the BIS monitor was kept covered, and the BIS values were recorded by another investigator.
Propofol infusion rate was altered by 20 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) if the systolic blood pressure (SBP) changed by more than 20\% of the baseline in the SP group and to achieve a BIS value between 45 and 60 in the BIS group. If there were other signs of inadequate anaesthesia (HR > 20\% of baseline or movement), additional dose of opioid (fentanyl or morphine) was administered. All unexpected intraoperative events requiring intervention were recorded and treated. Bradycardia (HR < 80\% of baseline) was treated by the injection of atropine. Children were not administered any type of regional block including caudal blocks for the surgical procedure.

The rate of propofol infusion was reduced by 50\% about 15 min before the end of surgery irrespective of the BIS values. The infusion was stopped 5 min before the end of surgery. Neuromuscular blockade was reversed with neostigmine (0.05 mg·kg\(^{-1}\)) and atropine (0.025 mg·kg\(^{-1}\)), and the trachea was extubated. Patients were transferred to the recovery room and monitored till they achieved the discharge criteria, i.e., a Steward score of 6 (15) (Table 1). Time from stopping the propofol infusion to eye opening, extubation, response to commands and attaining Steward score of 6 were recorded along with the BIS values at these times. Total amount of propofol used, duration of propofol infusion, duration of anaesthesia and surgery were also recorded. Duration of anaesthesia was defined as the time from the start of propofol bolus for induction to extubation of trachea; duration of surgery was defined as the time from surgical incision to the application of last suture.

The primary aim of the study was to observe whether propofol administration based on BIS monitoring caused a reduction in consumption of propofol. Assessment of recovery from anesthesia compared to the standard clinical practice in children was the secondary aim of the study.

Statistical analysis

Data was analyzed using SPSS software for windows version 10 (SPSS Inc., Chicago, IL, USA). Age, weight, HR, SBP, and duration of anesthesia, surgery and propofol infusion were compared between groups using Student’s \( t \)-test, whereas the BIS values were compared between groups using Mann–Whitney \( U \) test.

Sample size calculation

It was calculated that a sample size of 22 patients would be required in each study group to detect a 20\% difference in propofol consumption [average requirement of propofol 150 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) (SD 30)] with an alpha error of 0.05 and power of 90\%. To compensate for any exclusion, 25 patients were studied in each group.

Results

Fifty children were included in the study. The two groups were comparable with respect to the demographic data (Table 2). One patient (SP group) received lower propofol infusion rate owing to wrong dose calculation (Figure 1). There was no evidence of a difference in the total propofol consumption during maintenance of anesthesia in BIS group (108.6 ± 37.8 mcg·kg\(^{-1}\)·min\(^{-1}\)) and the SP group (106.6 ± 38.9 mcg·kg\(^{-1}\)·min\(^{-1}\)). The total morphine consumption was comparable between the two groups (Table 2). The number of patients requiring additional opioids was also similar in both the groups (two patients in BIS group compared to three patients in the SP group).

The two groups had comparable HR and SBP during the duration of the surgery (Figures 2 and 3). The median BIS values did not differ between the two groups over the duration of surgery. It ranged between 33–60 in the BIS group and 33–56 in the SP group (Figure 4). The mean propofol infusion rates at various time intervals during the course of the surgery were also similar in the two groups (Figure 5).
The time taken from reduction in propofol infusion rate to end of surgery was 9.2 ± 7.0 min in the BIS group and 12.4 ± 7.4 in the SP group. There was no evidence of a difference in the time interval.
between termination of anesthetic and return of consciousness between the groups (Log-Rank test) (Figure 6). The time to eye opening, time to extubation, time to response to commands, and time to achieve a Steward Recovery score of 6 were comparable in the two groups. The BIS values at these times (minutes) after start of propofol infusion were also similar in the two groups (Table 3).

Figure 6
Kaplan–Meier plot of the time interval between the termination of anesthetic and the return of consciousness was not significantly different between the groups. (Log-Rank test: \( P = 0.86 \)). Group SP (solid line): Standard Practice group; Group BIS (dashed line): BIS-guided group.

The number of children with hemodynamic adverse events such as hypertension (BIS = 5, SP = 5), hypotension (BIS = 6, SP = 7), and bradycardia (BIS = 8, SP = 6) was similar in the two groups.

Discussion
In adults, it has been established that the use of EEG-derived variables improves patient care in terms of decreased consumption of propofol, reduced incidence of awareness, and faster recovery (3–7). However, there is limited data in children regarding these benefits of EEG monitoring. We studied the effect of BIS monitoring on the consumption of propofol and recovery characteristics but did not find any evidence of a difference in propofol consumption and faster recovery when compared to the SP of anesthesia in children. The propofol infusion rate over the duration of surgery was also similar in the two groups.

Weber et al. (12) evaluated the impact of composite AEP index (cAAI) on propofol consumption and emergence times in children receiving propofol and remifentanil anesthesia. They found that cAAI monitoring results in reduced propofol consumption and faster emergence. In another study by the same authors, Narcotrend monitoring for the guidance
of propofol/remifentanil anesthesia in children resulted in reduced propofol consumption compared to conventional practice, but there was no effect on recovery from anesthesia (11).

There are a number of differences in the study design between our study and those of Weber et al., making it difficult to compare the results. Unlike our study, Weber et al. did not use muscle relaxants in their patients. Muscle relaxants abolish the electromyograph signal that may be falsely interpreted as an increase in anesthetic depth (16). They used remifentanil in their patients, which can alter the kinetics of propofol. When propofol is co-infused with remifentanil, measured drug values vary from the set target concentrations (17). Hoymork et al. (18) reported that propofol concentration was under-predicted by a median of 60% with a prediction error of 49% because the kinetics of propofol may be altered in the presence of remifentanil. Weber et al. used caudal or other nerve blocks in their patients in one of their studies. Regional blocks attenuate the effect of surgical stimulation on anesthetic requirement, resulting in less consumption of anesthetic agent (4). Also, it may be difficult to compare results because of the difference in the type of depth of anesthesia monitors used in the two studies.

The effect of BIS-guided sevoflurane consumption and recovery from anesthesia has been studied in children (4,19,20). Bannister et al. (4) found that the effect of BIS monitoring on sevoflurane use and recovery characteristics was different at different age groups. In the 0–6 months age group, BIS-guided anesthetic titration led to decreased anesthetic use but did not affect emergence or recovery times. In 6 months–3 years population, BIS did not reduce anesthetic requirements or speed recovery. In this group, the patients had received caudal block in addition to general anesthesia. In older children, again BIS-guided anesthetic management was associated with a significant reduction in anesthetic use, earlier emergence, and shorter recovery. Messieha et al. (19) also found that BIS-guided sevoflurane anesthesia resulted in substantially reduced recovery and discharge times. We did not find any evidence of a difference in recovery between the BIS and SP groups. This may be because our study had limited power to detect a difference in recovery between the two groups.

Normal pediatric EEG differs markedly from adult EEG, displaying more variation than adult EEG because electrical activity of brain changes with growth and development. In addition, BIS values have been assigned by monitoring adults at different depths of anesthesia (16). The effect of age on BIS has been a subject of many studies. Some authors have shown variation in BIS values with age using both inhalational agents as well as propofol (8,9,21,22). Liu et al. (13) observed that at loss of consciousness, at regaining of consciousness, and at the same stable concentrations of propofol, the BIS values were significantly higher in children than in adults. Tirel et al. (9) explored the relationship between age and BIS values at different plasma concentrations of propofol. The authors did not find any difference between BIS values under anesthesia with propofol 6 and 4 µg·ml⁻¹ but with propofol 2 µg·ml⁻¹, BIS was significantly different. A significant correlation between the age of children and the BIS values was found at propofol 2 µg·ml⁻¹ but not at 6 and 4 µg·ml⁻¹. This variation of BIS with age may be related to the difference in the pharmacodynamics of propofol in younger and older children (9). Thus,
caution should be used when adult algorithm of BIS 
monitoring is applied in children under propofol 
anesthesia.

A manual infusion pump and not a target con-
trolled infusion (TCI) pump was utilized in our 
study for the administration of propofol. There are 
differences in pharmacokinetics and pharmacody-
namics of propofol between adults and children 
because of growth and development. Although 
pharmacokinetic parameters can be programmed 
into a TCI device, pharmacodynamic measures in 
children remain poorly defined. Because of these 
differences, the algorithm used in adults for TCI may 
be less valid in children. We believe our infusion 
regimen was not substantially inferior to current TCI 
regimens for children.

The mean recovery times were slightly shorter in 
the BIS group, but the differences failed to reach 
statistical significance, so no evidence for any dif-
ference was found. It is perhaps not surprising that 
there was little difference in recovery times as 
similar amounts or propofol and opioids were used 
in each group. Using Narcotrend guidance for 
propofol administration, Weber et al. (11) found no 
difference in adverse events and time interval 
between the termination of anesthetic and the return 
of consciousness. The authors claimed this to be 
because of their study being underpowered to detect 
a difference in this secondary outcome. However, 
their study using cAAI monitoring in children 
showed shorter emergence times (12). The authors 
cautioned not to extrapolate the results of this study 
to other anesthesia techniques or other depth of 
anesthesia monitors.

We utilized Steward score for assessing the 
anesthetic recovery in our study. This score has 
never been formally validated for the pediatric 
patient population, but nonetheless is being widely 
accepted as a tool in the field of pediatric anesthesia 
research.

A limitation of this study was the use of three 
sensor device for BIS monitoring. This device does 
not use the new XP technology. Later, the newer 
version of the device became available but was not 
used as the algorithms used in the two devices may 
be different and may affect the results (16). Therefore, 
the results of our study apply to the type of device 
used, and some care must be taken when extrapol-
ating findings to newer versions of BIS monitors.

Awareness was not studied and is a limitation of 
our study as any reduction in propofol consumption 
must be balanced against the risk of awareness. 
Many children would be needed to exclude aware-
ness, which would be logistically difficult. Also, in 
the younger children, awareness assessment is dif-
ficult or impossible.

In our study, we reduced the infusion rate of 
propofol toward the end of surgery. BIS monitoring 
was however continued till the patient was awake. 
This was performed with the aim of hastening the 
recovery.

The practice of anesthesia differs in children, and 
there are arguments for and against the need for 
depth monitors in children. To be useful, the depth 
monitor should improve clinically important out-
comes. This has been demonstrated in some studies 
in children (4,11,12,19,20). The total quantity of drug 
used is less in children, and any advantage in terms 
of savings because of the use of BIS may be minimal. 
Also, the cost of advanced technology for routine 
anesthesia management may be an obstacle. On the 
other hand, it is plausible that EEG monitoring may 
enhance accurate drug delivery, reduce awareness, 
guide sedation in intensive care unit and improve 
safety of procedural sedation. However, our study 
failed to demonstrate any clinical benefit of depth 
monitoring.

In conclusion, the results of our study showed no 
benefit of BIS-guided administration of propofol on 
outcome in terms of anesthetic consumption or 
shorter recovery compared to standard anesthetic 
practice.

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