

Original Article

Correlation between Bispectral Index and Predicted Effect-site Concentration of Propofol in Different Levels of Target-Controlled, Propofol Induced Sedation in Healthy Volunteers

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Introduction: Bispectral Index is an objective tool to assess electroencephalographic activity and measure the effect of certain sedatives and hypnotics on the brain. In addition, there are certain subjective tools such as the observer's assessment of alertness and sedation which are used. The correlation between BIS and the concentration of propofol in the brain, and the relationship between these subjective and objective tools in assessing sedation levels are the subject of this study.

Methods: Thirty healthy volunteers enrolled in this prospective observational study. They were sedated with a target controlled infusion of propofol with an initial target of $0.8 \mu\text{g}\cdot\text{mL}^{-1}$ and an increase in target to $0.2 \mu\text{g}\cdot\text{mL}^{-1}$ ten minutes after equilibration of the predicted and set target concentrations. In each sedation score, the Bispectral Index value and predicted effect site concentration of propofol were recorded and analyzed. Analysis of variance and significant differences between groups were analyzed by paired t-test. Correlations between Bispectral Index and effect site concentration of propofol at each sedation score and the relationship of BIS and effect site concentration of propofol to each sedation score were assessed and analyzed by nonparametric Spearman's rho (ρ).

Results: The means of Bispectral Index and effect site concentration of propofol at each sedation score showed a significant difference with the following score. Additionally, Bispectral Index and effect site concentration of propofol showed a significant negative correlation in sedation scores 3 and 2 when inducing sedation. In other sedation scores or when reversing the sedation, no strong correlation was noted.

Conclusion: Both Bispectral Index and effect site concentration of propofol indicate a good estimate of sedation levels; however their correlations are significant and negative only at moderate and deep sedation levels, and during the induction of sedation.

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Introduction

It is a relatively common misconception amongst non-anesthesiologist physicians that sedation is safer than general

anesthesia and without serious complications. Many articles however, have described the complications of sedation even in well-staffed conditions.¹⁻³ In an attempt to perform an early diagnosis of diseases, many diagnostic and nonsurgical procedures are increasingly being performed in clinics and offices. In the operating room, it is usually anesthesiologists who administer sedatives and analgesics. It is their responsibility to monitor the patient's sedation state by subjective sedation scales such as the Observer's Assessment of Alertness and Sedation (OAA/S) and the

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Ramsy scale; or by objective monitoring tools which are usually electroencephalographic based such as the Bispectral Index (BIS) and Cerebral State Index (CSI). Anesthesiologists and CRNAs are familiar with these scales and monitors; however in outpatient offices those physicians who deal solely with diagnostic procedures may be not familiar with such monitoring tools and complications may develop. Also, sedation scales usually need a stimulus followed by a response to determine a level of consciousness which may repeatedly disturb the patient's calmness and the goals of sedation would not be achieved.

The capability of BIS to measure the sedative and hypnotic effects on the brain has been investigated in different studies.⁴⁻⁶ A BIS numerical value of 90 – 100 reflects an awake state, and values between 45 and 60 reflect hypnosis suitable for surgery (surgical anesthesia). There is an overall agreement in the mentioned scores, however between the scores of 60 to 90 there are no sharp and well defined scores with which to differentiate between different levels of clinical sedation. Although as listed in the Aspect Medical Company website, the range from 61 – 70 is cited as moderate sedation and 71 – 90 is light to moderate sedation (www.aspectmedical.com/professional/anesthesia/default.msp). Furthermore, the large interindividual and intraindividual variability in BIS scores reduces its ability to predict the depth of sedation in different subjects, thereby limiting its usefulness.^{7,8}

As we know, patients with propofol induced sedation may rapidly go into deeper or

lighter levels of sedation if the plasmatic or brain propofol concentrations change. Because of the narrow therapeutic window of propofol, an excessive depth of sedation may be associated with clinically significant cardiovascular and respiratory depression; whereas lighter levels of sedation may be associated with intraoperative recall.^{9,10}

Some investigators have compared a number of subjective clinical scoring systems with BIS, an objective assessment tool.¹¹⁻¹⁴ Few studies have included a correlation between the results obtained with both subjective and objective assessment techniques.^{15,16} On the other hand, using a different subjective scoring for sedation requires disturbing patients in order to catch a response. Hence if the physician could trust the objective sedation tools, patients could be left sedated and relaxed during surgical procedures.

The general goal of this study is to establish a correlation between a reliable subjective measure, the Modified Observer's Assessment of Alertness/Sedation Score (MOAA/S) as developed by Chernik et al.¹⁷ (Table 1) and an objective tool, BIS, for monitoring different scores of sedation in healthy volunteers. The responsiveness component of OAA/S has been investigated in different studies.^{18,19} Our study is novel in that the correlation between BIS and the predicted concentration of effect site propofol (Cep) as well as the correlation between BIS and OAA/S are studied in sedation levels produced by a target-controlled infusion (TCI) technique.

Table 1. Modified observer's assessment of alertness and sedation score

Score	Sedation level	Responsiveness	Speech	Facial expression	Eyes
5	Alert	Responds readily to name	Normal	Normal	Clear, no ptosis
4	Light	Lethargic response to name	Mild slowing	Mild relaxation	Glazed or mild ptosis
3	Moderate	Response only after name is called loudly	Slurring or prominent slowing	Marked relaxation	Glazed and marked ptosis
2	Deep	Response only after mild prodding or shaking	Few recognizable words	—	—
1	Deep sleep	Response only after painful stimulus	—	—	—

Patients and Methods

This was a prospective observational study conducted with 30 healthy volunteers in a large educational hospital. The study protocol was approved by the medical ethical review board at our university.

Participants were informed of the study by advertisements placed in different faculties in the university. Thirty healthy volunteers were screened and gave written informed consent to participate. This study consisted of a single visit and participants were paid for their involvement.

All volunteers underwent a history and physical examination before being enrolled in the study. Inclusion criteria were age >18 years and American Society of Anesthesiologists (ASA) classification I-II. The exclusion criteria were: known neurological disorders including psychoactive or anticonvulsant medications, chronic alcohol, illicit drug or medication abuse, ASA class greater than II, body mass index (BMI) >30, women who were pregnant, and any previous adverse reactions to propofol, soybeans and eggs. Before the study visit, subjects were required to fast for at least 8 hours. Subjects' height and weight were measured and body surface area (BSA) and BMI were calculated automatically by TCI pump software and recorded on a checklist sheet. Baseline values for arterial blood pressure, heart rate and oxygen saturation were taken and continuous electrocardiogram monitoring was recorded.

On the morning of the study, a 20G intravenous cannula was inserted into a large antecubital vein and ringer's lactate solution 10ml.kg^{-1} was administered during 30 minute period for all subjects. In order to insure participants' safety, the study was performed in a fully equipped, standard operating room.

Prior to attaching the BIS sensor to the forehead, the skin was cleaned with alcohol. Each sensor consisted of a single piece with four marked electrodes. The sensor was then connected to an Aspect Medical Systems, Inc.

(Newton, MA), A-2000 XP monitor version 3.23 USA. If the impedance of the electrodes was greater than $5\text{K}\Omega$ the inside of the electrodes was applied to the forehead with conductive gel. The smoothing time of the BIS monitor was set at 15s. To decrease artifacts, subjects were asked to close their eyes and not speak or move during the brief BIS assessment periods. As BIS values were affected by noise disturbances at light levels of propofol sedation, all non attendant personnel were asked to leave the room and any unnecessary lights turned off.^{20,21} All subjects received pure oxygen via a nasal probe to maintain O_2 saturation levels above 95%. Propofol 1%; (Fresenius Kabi Company, Germany) was administered via a TCI pump with an effect-site target concentration using the Schnider pharmacokinetic model.²² The propofol infusion was performed using a Fresenius Modular DPS infusion pump connected to a Base Prima with an integrated Orchestra TCI system (Fresenius Kabi Company, Orchestra Base Prima and DPS Module System, France). The initial Cep set at $0.8\ \mu\text{g.mL}^{-1}$ and was altered after equilibrium between the predicted and set concentration was determined (not more than $0.2\ \mu\text{g.mL}^{-1}$ at 3 minute intervals) until a sedation score of 4 was reached. The sedation evaluation was based upon a standard five-point OAA/S scoring scale (Table 1). The OAA/S score was used because it has shown good correlation with sedation in previous investigations.¹⁷

One minute after equilibration of the initial target concentration, OAA/S was assessed by an expert anesthesiologist assessor who was blinded to Cep and BIS. If necessary, the target was subsequently increased an additional $0.2\ \mu\text{g.mL}^{-1}$ by another anesthesiologist. One assessor performed all objective sedation assessments. When an OAA/S score of 4 was determined, BIS and Cep were recorded and after 10 minutes at that level. The same increasing in target concentration repeated and BIS and Cep at OAA/S scores 3 and 2 were also obtained, then the direction of assessment was reversed

and BIS and Cep were recorded with $0.2\mu\text{g}\cdot\text{mL}^{-1}$ decrease in target as well as achieving OAA/S scores 3 and 4 with the same conditions of the study.

In order to reach the goals of the study, we undertook three steps: first Cep was calculated as predicted by the TCI pump at the 4, 3, and 2 OAA/S sedation scores as a translation of mild, moderate and deep sedation; both when inducing and reversing sedation. Second the mean BIS value in these sedation scores was determined and thirdly, to interpret the relation between the BIS value and each sedation score, Cep and each sedation score, and the correlation between the BIS value and Cep in each sedation score.

Mean values and standard deviation of BIS and Cep were determined at each OAA/S score during induction and recovery from sedation. The correlation between BIS and Cep at each OAA/S score was estimated by nonparametric Spearman's rho (ρ). The significant levels of Cep and BIS changes at each sedation score were analyzed by the test of within-subjects analysis of variance (repeated measures). Significant differences between the two groups were analyzed by paired *t*-test. A relevant change in the BIS value was assessed 10 score and a sample size of 25 was suggested. With the probability of exclusion of some subjects during the study, we enrolled 30 volunteers in this study.

Results

All subjects maintained vital signs in the normal range during the study period and none experienced O_2 saturation below 97%. Two subjects were excluded from the study because of a signal quality index (SQI) below 50%, an interruption of BIS recording during the test, and missing data. A total of 140 BIS values

Table 2. Subjects' characteristics

	Mean± SD (Range)
Age (years)	23.1±3.6(19–36)
Weight (kg)	65.8±9.6(43–81)
Height (cm)	169.1±9.0(146–186)
BMI (kg/m ²)	22.7±2.5(19.30–27.9)
BSA (m ²)	1.7±0.2(1.44–2.6)

BMI=body mass index; BSA=body surface area

and 140 target concentrations were collected corresponding to 5 sedation scores in 28 volunteers. Subjects' characteristics have been shown in Table 2. As shown in the scatter plot of Figure 1, the negative correlation of BIS and Cep was statistically significant at sedation scores of 3 (Spearman's rho= -0.441, $P=0.019$) and 2 (Spearman's rho= -0.491, $P=0.008$) when sedation was induced but not in other studied sedation levels.

The mean, standard deviation and range of Cep and BIS index at 5 OAA/S scores have been displayed in Table 3. These data show that increasing the depth of sedation (from score 4 to 2) parallels the progressive increase of Cep and decreasing the depth of sedation (from score 2 to 4) parallels the progressive decrease of Cep. At the same time, an increase in sedation level was associated with a progressive decrease of BIS and decrease in the sedation level was associated with a progressive increase of BIS.

Results of within-subjects analysis of variance (repeated measures) indicated that the mean Cep in sedation scores 4 and 3 ($P<0.001$), and sedation scores 3 and 2 ($P<0.001$) showed significant differences during sedation induction and conversely the mean Cep in sedation scores 2 and 3 ($P<0.001$), and 3 and 4 ($P<0.001$) showed significant differences during reversing sedation. Therefore, Cep in each sedation score differs significantly with the next sedation score and the results of within-subjects test (repeated measures) indicated that the mean BIS at sedation scores 4 and 3 ($P<0.001$), and sedation scores 3 and 2 ($P<0.001$) showed significant differences during sedation induction. Conversely, the mean BIS at sedation scores 2 and 3 ($P<0.001$), and sedation scores 3 and 4 ($P<0.001$) were significantly different during sedation reversal. Therefore, BIS in every sedation score differs significantly with the next sedation score.

Discussion

In this study we have attempted to display

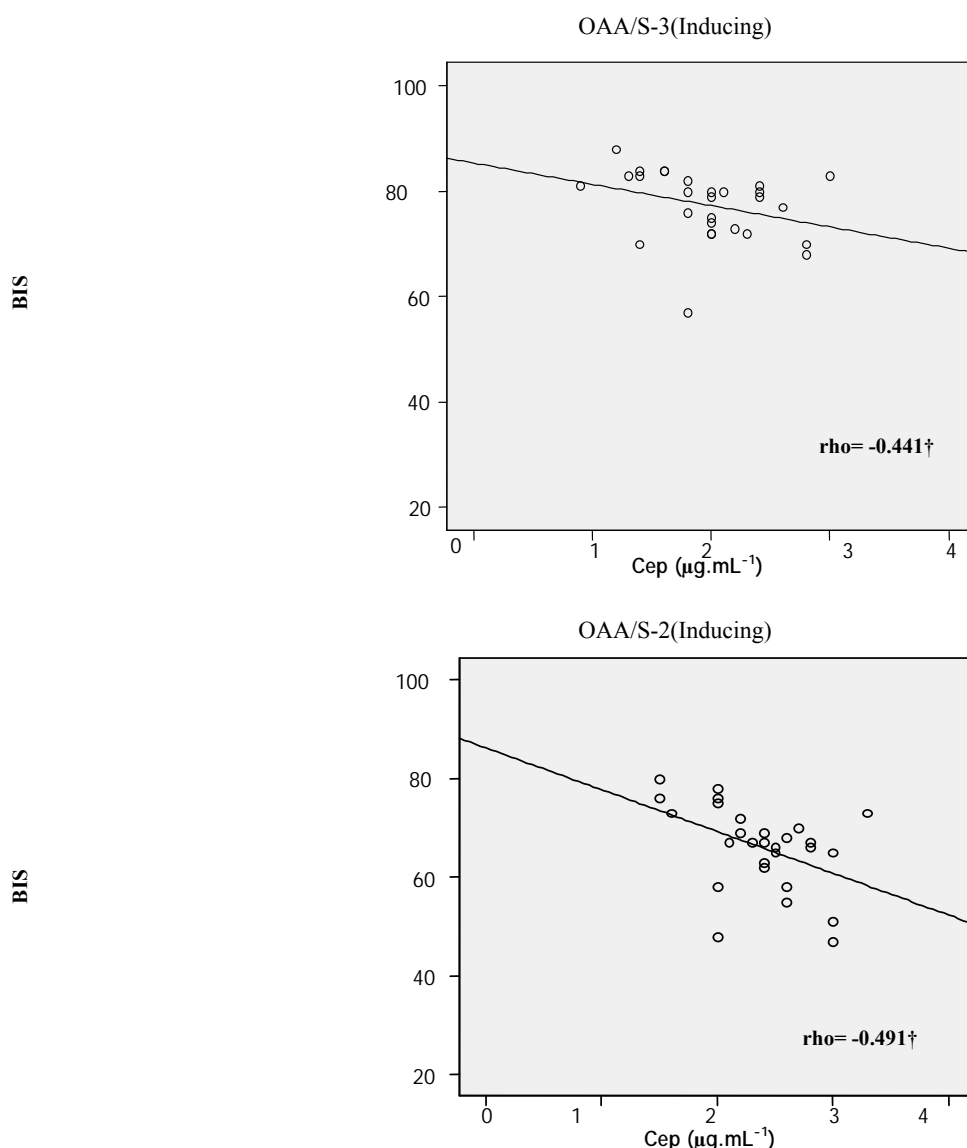


Figure 1. Correlation between BIS and Cep in sedation scores 3 and 2 during induction of sedation.

†Negative correlation is significant; BIS=Bispectral Index; Cep=effect site concentration of propofol; OAA/S=observer's 'assessment of alertness and sedation

a correlation between BIS as an electroencephalogram (EEG) based monitor that could continuously determine the level of sedation and Cep as a predicted target reflecting the drug effect at different levels of sedation as assessed by OAA/S. Propofol is increasingly used to

induce and maintain sedation states for various procedures such as endoscopic examinations,²³ pediatric diagnostic examinations,²⁴ dental extractions,²⁵ and even for critically ill patients.^{26,27} Sedation, however, is a mysterious state ranging from anxiolysis

Table 3. Mean, range and standard deviation of Cep and BIS at different OAA/S scores when inducing and reversing sedation

Level of sedation	Min Cep	Max Cep	Mean (SD)	Min BIS	Max BIS	Mean (SD)
OAA/S 4 (inducing)	0.8	2.40	1.32(0.41)	74	98	89.50(6.68)
OAA/S 3(inducing)	0.9	3.00	1.96(0.51)	57	88	77.39(6.54)
OAA/S 2	1.50	3.30	2.37(0.45)	47	80	66.10(8.56)
OAA/S 3(reversing)	0.8	3.00	1.72(0.56)	48	94	73.92(9.99)
OAA/S 4(reversing)	0.6	2.10	1.11(0.42)	76	98	86.53(6.93)

Cep=predicted effect-site concentration of propofol; BIS=Bispectral Index

through general anesthesia. Problems in this state should be recognized rapidly and managed appropriately in order to prevent cardiac arrest, brain damage and death. Complications usually seen with sedation are respiratory, cardiac and systemic such as laryngospasms, hypoxemia, dyspnea, nausea and vomiting, arrhythmia, hypotension, and death.

Today modern infusion pumps are available and propofol is usually delivered as a continuous infusion instead of intermittent bolus doses. One of the newest devices is the TCI pump which, since 1996, is available worldwide with the exception of North America. These pumps use pharmacokinetic models to deliver pre-determined target concentrations of drugs in plasma or brain. Pharmacokinetic models for propofol TCI are varied and many studies have described the target-controlled infusion of propofol in anesthetic doses,^{28,29} but publications about sedative propofol doses used by target-controlled techniques are limited. We have used the Fresenius TCI pump for this study because this model is available in our institute and is used daily in clinical practice for simultaneous TCI of propofol, remifentanyl and sufentanil. The Schnider pharmacokinetic model has been used because of a more rapid plasmatic and effect-site concentration equilibration than the Marsh model.²²

In this study we found levels of sedation described with a subjective assessment tool (OAA/S) accompanying with wide range of Cep and BIS.

Also this study demonstrates that the mean Cep concentrations/values for each level of sedation is significantly different with the following level. Hence Cep at sedation score 4 is significantly less than score 3, and Cep at score 3 is less than score 2 (sedation induction) and conversely, during reversal of sedation, Cep at a sedation score of 2 is greater than score 3 and Cep at sedation score 3 is more than score 4. This can be concluded to mean BIS values for each level of sedation which would be significantly different with the

following level. For example, the BIS value at sedation score 4 is significantly more than 3 and the BIS value at score 3 is more than score 2 (when inducing the sedation). Conversely the BIS value at sedation score 2 is less than 3 and BIS at sedation score 3 is more than score 4 when sedation is reversed. Within the BIS range of 61 – 70, clinical sedation scores have a wide distribution range from an OAA/S score 2 to 3. Within the 71 – 90 range BIS clinical sedation scores show an even wider distribution, from OAA/S 2 to 4. According to the monitor manufacturer's instruction scores, a value greater than 90 represents awake states, however we have found these scores at OAA/S 3 and 4.

This means individuals do not respond to propofol sedation doses identically and despite similar clinical sedation states the brain concentration of propofol and BIS may vary amongst different cases. We know that the precision of TCI pumps may play a role in this state. Also, pharmacokinetic models are obtained from a population's pharmacokinetic analysis in order to optimize its performance and may not include characteristics of all people. The capability of these models to predict targets precisely depends on multiple variables such as gender, age, height, weight, health status and other unknown variables which make interindividual and intraindividual differences in response to models. There are several studies with controversial conclusions about the correlation between BIS and clinical assessments of sedation. Weaver and co workers²⁰ found a moderate correlation (Spearman 0.59) between BIS and two different clinical sedation scales (OAA/S and Continuum Depth of Sedation). Mean BIS scores in their study were not significantly different for those with sedation complications versus those without complications; hence the correlation was not strong enough to be used reliably in a clinical setting. Gills and co workers³⁰ also found that BIS monitoring was unable to effectively discriminate between mild to moderate and moderate to deep sedation in their study patients (Spearman

0.69). Liu and coworkers found that with increasing depths of sedation (assessed with OAA/S) the BIS decreased and during recovery from propofol sedation, BIS increased progressively with good correlation between BIS and OAA/S when inducing (Spearman 0.744) and reversing (Spearman 0.705) from propofol sedation. The mentioned study was undertaken with intermittent bolus doses of propofol, 10 – 20 mg i.v. each 5 – 10 minutes, instead of a continuous infusion which may produce fluctuations in the sedation state leading to inaccuracy in assessment of the depth of sedation.³¹ There are several other studies whose findings are comparable with ours.^{14,32-35} However, there are other studies whose findings do not confirm our results.^{12,36-40}

Administration of opioid analgesics and or sedative/anxiolytics such as benzodiazepines could alter the pharmacokinetic and pharmacodynamic responses of patients when propofol is administered. This is the scenario most patients who are scheduled for surgical procedures and simultaneously enroll in clinical studies. Such premedications lower the propofol target concentration that is needed to decrease BIS or change the patients' sedation states. Subjects who enrolled in our study were not premedicated hence we can rely more on the accepted results. On the other hand, Cep is a rough estimate of the true effect site concentration, which may differ up to 30% with the true brain concentration and this is a pitfall when TCI is used. Indeed in clinical studies, investigators may be obligated to change the target concentration of propofol before complete equilibration between the predicted and set target concentration because of the patient's clinical condition, which was not necessary in our study. These are some points which could explain the discrepancies in conclusions amongst different studies. We believe each study should be judged under its own conditions. In our study, BIS didn't correlate with subjective sedation scores (OAA/S) but correlated with Cep only in moderate and deep sedation levels during

sedation induction.

Since it is not practical to use clinical sedation scales by non-anesthesiologist physicians, they may tend to use monitors as an objective measure of the level of sedation. Hence during diagnostic procedures or office based surgeries patients may move from one plane of sedation to another plane even to the level of general anesthesia without physician awareness.

Cep at different levels of sedation also shows a similar pattern and a huge overlap but there is not a well-defined border for propofol concentration to produce a desired clinical sedation plane. Correlation between BIS and Cep were significant only in moderate to deep clinical sedation scores. Therefore, one can say that with a deeper clinical sedation more correlation between BIS and Cep was seen. Unfortunately deep sedation levels aren't the sedation levels which non-anesthesiologist physicians seek.

Conclusion

This study demonstrated that good correlation was seen between BIS value and Cep in only moderate to deep sedation scores. This correlation, however, is not sufficient to estimate the level of sedation because of the wide range in each sedation score and physicians cannot use them as the sole tools for differentiation of sedation levels instead of subjective assessment tools. Based on this study we conclude that BIS does not reliably assess sedation levels, especially in the light to moderate levels of sedation. Physicians should always look for clinical signs of oversedation and undersedation, of which the former is more dangerous. Although the flexibility of TCI permits adjustment of a stable sedative state and allows anesthesiologists to deliver propofol in a single step for sedation with fewer human intervention; BIS and Cep showed a strong negative correlation only in the moderate and deep sedation levels when inducing sedation. Physicians can only weakly rely on them as an indicator of the level of sedation.

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