Prospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(4) 1–10

DOI: 10.1177/0300060519893165
journals.sagepub.com/home/imr
SAGE

Efficacy of the bispectral index and Observer's Assessment of Alertness/Sedation Scale in monitoring sedation during spinal anesthesia: A randomized clinical trial

Tae Wan Lim[1], Yi Hwa Choi[1], Jong Yeop Kim[2], Jong Bum Choi[2], Soo Kyung Lee[1], Eun Ji Youn[1] and Jun Suck Lee[1]

Abstract

Objective: The bispectral index (BIS) has been used to monitor sedation during spinal anesthesia. We evaluated the correlation between BIS and the Observer's Assessment of Alertness/Sedation Scale (OAA/S) in patients sedated with dexmedetomidine, propofol, or midazolam.

Methods: This prospective, randomized study included 46 patients scheduled for knee arthroplasty under spinal anesthesia with sedation. The patients were randomized to receive sedation with dexmedetomidine (n = 15), propofol (n = 15), or midazolam (n = 16). Correlation between BIS and OAA/S was assessed during sedation in the three groups.

Results: A linear correlation was observed between BIS and OAA/S, and there was no significant difference in BIS score between the groups during mild to moderate sedation status (OAA/S 3–5). During deep sedation (OAA/S 1–2), the BIS score in the midazolam group was significantly higher than that in the propofol and dexmedetomidine groups (74.4 ± 11.9 vs 67.7 ± 9.5 vs 62.6 ± 12.2).

Conclusions: BIS values differed at the same level of sedation between different sedative agents. Objective sedation scores should therefore be used in combination with BIS values for the assessment of sedation levels during spinal anesthesia.

[1]Department of Anesthesiology and Pain Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea
[2]Department of Anesthesiology and Pain Medicine, Ajou University School of Medicine, Suwon, Republic of Korea

Corresponding author:
Yi Hwa Choi, Department of Anesthesiology and Pain Medicine, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, 22 Gwanpyeong-ro, 170 Beon-gil, Dongan-gu, Anyang 14068, Republic of Korea.
Email: pcyhchoi@hallym.or.kr

Keywords
Consciousness monitors, anesthesia, spinal, propofol, midazolam, dexmedetomidine

Date received: 7 May 2019; accepted: 13 November 2019

Introduction

Intraoperative sedation is an important component of regional and local anesthetic techniques. Sedation allows the smooth conduct of surgery and improves patient satisfaction by allaying fear and anxiety during procedures under regional and local anesthesia.

Inadequate intraoperative sedation may cause patient movement that can interfere with the surgical procedure. Furthermore, it may cause physical and mental stress, discomfort, and anxiety among patients. Therefore, continuous monitoring of the level of sedation during spinal anesthesia is essential to eliminate anxiety and to ensure smooth performance of the surgical procedure. Conventional methods to determine the adequacy of sedation rely on subjective assessment using the Observer's Assessment of Alertness/Sedation Scale (OAA/S).[1] Assessment is carried out intermittently depending on the patient's response to either verbal or physical stimuli. However, the use of such stimuli for assessment can cause patient discomfort and interfere with the surgical procedure.[2]

The bispectral index (BIS) is a continuous noninvasive electroencephalographic (EEG) monitor that has been developed to monitor the hypnotic state during sedation and anesthesia.[3–6] Specifically, BIS has been used as a measure of hypnosis during general anesthesia. Several previous reports have attempted to correlate or predict levels of sedation in patients or volunteers receiving volatile agents, propofol,[5] midazolam,[7] opioids,[8] or nitrous oxide.[9] BIS monitoring has been used to guide sedation during spinal anesthesia as an objective method of monitoring[6,10,11] and is considered a useful monitoring system to maintain an adequate level of sedation. However, the results from previous studies have been conflicting regarding the correlation between BIS and sedation levels.[12–15] Furthermore, BIS has not been evaluated in the comparison of different sedative agents.[10]

The aim of this study was to investigate the correlation between BIS values and OAA/S scores during sedation with dexmedetomidine, propofol, and midazolam and to compare the efficacy of BIS to predict the depth of sedation obtained using these drugs.

Methods

This prospective, randomized, patient-blinded study was carried out from 5 July 2016 to 28 February 2018 after obtaining approval from the institutional review board of University Sacred Heart Hospital (5 July 2016, reference numbers: IORG0004993, IRB00005 the Hallym 964). The study was registered at ClinicalTrials.gov (NCT03399019). Written informed consent was obtained from participating patients or their legal guardians.

Patients with American Society of Anesthesiology physical status I or II who were scheduled for knee arthroscopic surgery under spinal anesthesia with intravenous sedation were eligible to participate. Continuous BIS monitoring was carried out in all patients. Patients received sedation with dexmedetomidine (n = 15), propofol (n = 15), or midazolam (n = 16) according to a computer-generated randomization sequence. We excluded patients

with a history of adverse reaction to dexmedetomidine, propofol, or midazolam; contraindications to sedative use, including cardiac dysfunction; history of severe hepatic or renal disease; decreased circulating blood volume; hemodynamic instability; difficulty in communication; or at risk of aspiration. We also excluded patients who experienced inadequate spinal anesthesia as well as those converted to general anesthesia due to uncontrollable anxiety. No premedication was administered prior to anesthesia.

Routine physiological monitoring included noninvasive arterial blood pressure measurement, heart rate measurement, arterial oxyhemoglobin saturation (SaO_2) measurement, capnography, and electrocardiography. BIS electrodes (A-3000 EEG BIS monitor, Aspect Medical systems, Norwood, MA, USA) were placed on the forehead of each patient after cleansing of the skin with an alcohol-impregnated skin wipe to reduce electrode impedance. Patients were also connected to a CARESCAPE Monitor B650 for measurement of the Surgical Pleth Index (SPI, General Electric, Helsinki, Finland).

BIS measurement commenced prior to the administration of sedatives. Following a baseline hemodynamic assessment, baseline BIS values were obtained without disturbance over 10 minutes. A warming blanket was used to prevent electromyographic artifacts attributable to shivering.

Spinal anesthesia was performed without sedation in the lateral decubitus position at the L3–4 or L4–5 interspace using a 25-gauge Quincke needle (Hakko, Nagano, Japan) and 0.5% hyperbaric bupivacaine (Reyon, Seoul, Korea) at a dose of 9 to 13 mg depending on patient height. Patients were placed in the supine position immediately after spinal anesthesia. After a 10-minute interval, the level of sensory block was determined by the application of a cold stimulus using an alcohol swab. Motor block was assessed using the Bromage scale. Surgery commenced when the onset of sensory block at T12 was observed, with sedation according to the randomization group.

A face mask was applied prior to administration of study drug and was fixed to the head using a rubber strap. OAA/S, BIS scores, and baseline hemodynamic parameters were recorded prior to commencing sedation. BIS values were recorded before OAA/S evaluation to minimize the effect of verbal or physical stimuli used during OAA/S assessment. Sedation was titrated to an OAA/S score of 3.

In the dexmedetomidine group, a loading dose of dexmedetomidine 1 μg/kg was administered intravenously over 10 minutes followed by a maintenance infusion of 0.2 to 0.7 μg/kg/h. In the propofol group, intravenous infusion was commenced at 50 to 75 μg/kg/minute for 10 minutes, followed by titration of the infusion between 0.75 and 3 μg/kg/minute for 10 minutes. In the midazolam group, following an initial bolus of 0.05 mg/kg, repeat boluses of 0.01 mg/kg were administered to achieve the desired level of sedation. The maximum dose of midazolam was limited to 2.5 mg during a 5-minute interval in patients aged 60 years or older.

Intraoperative use of fentanyl was allowed if the patient felt pain at the surgical site. In cases of anxiety, agitation, or excessive patient movement, propofol administration was permitted in all groups. The level of sedation was evaluated using OAA/S score and BIS values at 5, 15, 30, 45, 60, and 90 minutes after commencement of sedation and at the end of surgery. The primary outcome of the study was the correlation between OAA/S and BIS scores for each study group. Secondary outcomes included the discriminating performance of BIS for OAA/S, and clinically adverse events related to study medication use. Adverse effects were recorded by an

independent observer. Patients were discharged from the post-anesthesia care unit (PACU) when the post-anesthetic Aldrete recovery score was $\geq$9. The duration of PACU stay was also recorded.

Statistical analysis

Categorical variables are summarized as frequencies with percentages, whereas continuous variables are summarized as the median and interquartile range or mean and standard deviation as appropriate. The Shapiro–Wilk test was used to assess the normal distribution of continuous variables. Categorical variables were compared using the chi-square test, whereas continuous variables were compared using analysis of variance with post-hoc analysis with Tukey's method or a Wilcoxon rank-sum test, as appropriate. Receiver-operating characteristics (ROC) analysis was used to assess the discriminating performance of each variable. Pairwise comparisons between ROC curves were made using the method of Delong.[16] We estimated the effect size based on the correlation coefficient between BIS and OAA/S. Assumption of the correlation between BIS and OAA/S was estimated to be 0.7, as reported previously.[17] We also sought to detect the effect size of correlation with 5% α-error and 80% statistical power. Thus, we calculated that 15 patients were needed for each group, with an estimated dropout rate of 10%. All statistical analyses were performed using SPSS version 24.0 (IBM Corp. Armonk, NY). All P-values were two-sided, and P-values <0.05 were considered statistically significant.

Results

Fifty patients were enrolled according to the inclusion criteria. Four patients were subsequently excluded because of conversion to general anesthesia due to agitation and inappropriate spinal anesthesia. Forty-six patients were therefore enrolled and randomized to the midazolam (n = 16), propofol (n = 15), or dexmedetomidine (n = 15) group (Figure 1). The baseline characteristics of patients are summarized in Table 1. There was a trend toward older age in the midazolam group and more female patients in the propofol group. However, the differences were not statistically significant. The duration of surgery and anesthesia was not significantly different between groups. However, the duration of stay in the PACU was longer in the dexmedetomidine group ($p = 0.021$). Rescue propofol was more frequently used in the propofol group. One patient in the midazolam group and four patients in the propofol group required supplemental doses of propofol. No patient required supplemental fentanyl intraoperatively. The changes in vital parameters according to the depth of anesthesia are summarized in Table 2. During anesthesia, the mean arterial pressure was significantly higher ($p < 0.05$) and heart rates tended to be lower in the dexmedetomidine group. Oxygen saturation was not significantly different between the groups at any depth of anesthesia. The cumulative doses of dexmedetomidine, midazolam, and propofol were 113.51 μg (interquartile range [IQR] 65.0–327.4), 3.0 mg (2.0–3.7), and 268.8 mg (120.9–390.9), respectively.

The main study outcome, correlation between BIS values and OAA/S scores, is plotted in Figure 2. In general, linear correlation was observed between BIS values and OAA/S scores ($r=0.748$, $p<0.001$). There was no significant difference in BIS values between the groups at mild to moderate sedation levels (OAA/S 3–5). However, during deep sedation (OAA/S 1–2), BIS values in the midazolam group were significantly higher than those in the propofol and dexmedetomidine groups ($p = 0.017$). In the midazolam group, the mean BIS

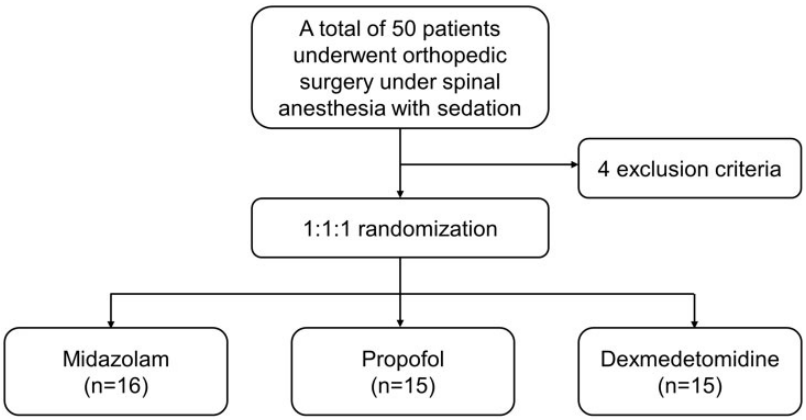

Figure 1. Study flow diagram.

Table 1. Patient characteristics.

	Midazolam	Propofol	Dexmedetomidine	P-value
Age (years ± SD)	51.2 ± 10.8	42.9 ± 18.1	44.1 ± 12.1	0.251
Sex (male)	6 (40)	12 (80)	8 (50)	0.070
ASA physical status, number (%)				0.125
1	6 (40)	4 (27)	10 (62.5)	
2	9 (60)	11 (73.3)	6 (37.5)	
Duration of surgery (minutes ± SD)	62.5 ± 45.9	77.1 ± 44.9	64.6 ± 28.5	0.605
Duration of anesthesia (minutes ± SD)	89.1 ± 31.5	95.0 ± 29.9	88.5 ± 28.5	0.832
PACU time (minutes ± SD)	22.1 ± 7.5	19.6 ± 7.2	37.3 ± 27.1	0.021
Rescue propofol, number (%)	1 (6.7)	4 (26.7)	0 (0)	0.048
Bradycardia, number (%)	3 (20)	2 (13.3)	8 (50)	0.053

ASA: American Society of Anesthesiology; PACU: post-anesthesia care unit.

values at OAA/S 3 and OAA/S 1 or 2 were not significantly different (77.9 ± 6.5 vs. 74.4 ± 11.9, $p = 0.302$). Although not statistically significant, BIS values in the dexmedetomidine group at OAA/S 3 (69.3 ± 18.5) were lower than those in the propofol (77.9 ± 7.5) and midazolam (75.8 ± 8.1) groups.

The discriminating performance of BIS values for deep sedation status (OAA/S 1 or 2) is summarized in Figure 3 and Table 3. In general, BIS values showed excellent performance for discriminating deep sedation, with an AUC value of 0.87 (95% CI 0.82–0.92). For individual drugs, the discriminating performance of BIS was excellent for propofol (AUC 0.95, 95% CI 0.88–0.98) and dexmedetomidine (AUC 0.87, 95% CI 0.82–0.92), but was significantly lower for midazolam (AUC 0.79, 95% CI 0.65–0.94). The optimal cut-off values for deep sedation with midazolam, propofol, and dexmedetomidine were 75 (sensitivity [SN] 89%, specificity [SP] 63.6%), 79 (SN 82.2%, SP 93.3%), and 83 (SN 72.4%, SP 100%), respectively. Bradycardia (heart rate <60/minute) was observed more frequently in the

Table 2. Intra-operative parameters during anesthesia.

	Midazolam	Propofol	Dexmedetomidine	P-value
Mean arterial pressure				
OAA/S 5	96.8 ± 14.0	93.8 ± 15.5	100.5 ± 13.6	0.04
OAA/S 4	86.9 ± 7.6	82.9 ± 9.4	98.0 ± 15.8	<0.001
OAA/S 3	87.1 ± 12.3	79.4 ± 9.5	103.8 ± 16.7	<0.001
OAA/S 1–2	86.4 ± 11.9	81.7 ± 14.1	98.1 ± 15.2	0.002
Heart rate				
OAA/S 5	66.6 ± 11.3	65.8 ± 14.7	64.8 ± 11.7	0.758
OAA/S 4	61.4 ± 13.1	56.5 ± 11.2	53.9 ± 6.0	0.06
OAA/S 3	63.1 ± 13.8	59.2 ± 11.2	54.7 ± 7.6	0.093
OAA/S 1–2	61.8 ± 12.2	59.3 ± 12.6	54.7 ± 5.7	0.081
Oxygen saturation				
OAA/S 5	98.7 ± 1.9	99.0 ± 1.4	98.6 ± 1.7	0.351
OAA/S 4	99.4 ± 0.7	99.3 ± 1.1	99.4 ± 0.8	0.823
OAA/S 3	99.3 ± 0.7	98.9 ± 1.0	99.3 ± 1.1	0.442
OAA/S 1–2	99.4 ± 0.7	99.0 ± 0.9	99.2 ± 0.8	0.457
BIS				
OAA/S 5	92.6 ± 6.4	93.1 ± 5.9	92.4 ± 63.	0.754
OAA/S 4	80.6 ± 6.9	80.7 ± 5.9	81.5 ± 12.3	0.936
OAA/S 3	77.9 ± 7.5	75.8 ± 8.1	69.3 ± 18.5	0.087
OAA/S 1–2	74.4 ± 11.9	67.7 ± 9.5	62.6 ± 12.2	0.017

OAA/S: Observer's Assessment of Alertness/Sedation Scale; BIS: bispectral index.

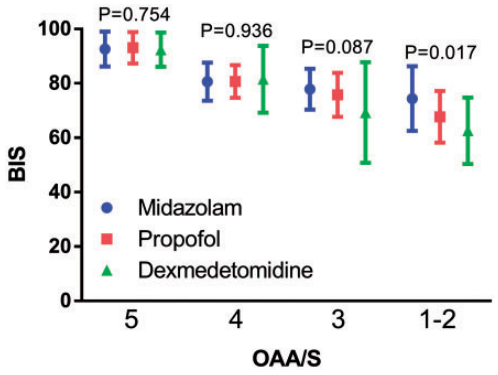

Figure 2. Bispectral index values versus depth of sedation by OAA/S score. OAA/S: Observer's Assessment of Alertness/Sedation Scale.

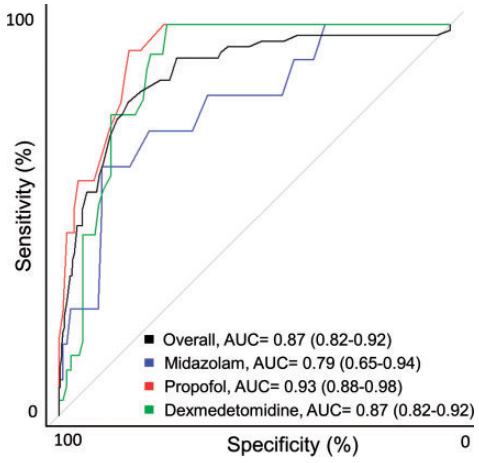

Figure 3. Analysis of receiver-operating characteristics for deep sedation (bispectral index value ≤2) for each drug.

dexmedetomidine group and was treated with 0.5 mg of intravenous atropine for <50 minute. One episode of hypotension was reported in the propofol group and was responsive to 10 mg of intravenous ephedrine. No other side effects were noted.

Discussion

Our results demonstrated that BIS values were insufficiently sensitive to accurately

Table 3. Discriminating performance, best cut-off value, sensitivity, and specificity of different sedative agents.

	AUC	95% CI	Cut-off value	Sensitivity	Specificity	PPV	NPV
Midazolam	0.79	0.65–0.94	75	89	63.6	95.700	38.9
Propofol	0.93	0.88–0.98	79	82.2	93.3	98.800	43.8
Dexmedetomidine	0.87	0.82–0.92	83	72.4	100	100.000	49.1

AUC: area under the curve; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

reflect the depth of sedation in the midazolam group. The present study investigated whether BIS, which has previously been demonstrated as a reliable measure of hypnosis during general anesthesia,[18] might inappropriately reflect the degree of sedation during spinal anesthesia with sedation. The BIS value for loss of responsiveness to verbal stimulation (OAA/S score <2) is 64 to 65, which is considered to reflect superficial anesthesia or a light hypnotic state.[4,19]

BIS is widely used for continuous monitoring of sedation[20,21] and is a well-established method for assessing the level of sedation in current anesthetic practice. Jo et al.[21] defined a BIS value of <85 as a reference for moderate sedation. However, BIS monitoring has not yet been shown to represent a precise monitoring modality for the assessment of level of sedation, in contrast to its established accuracy in the monitoring of the depth of anesthesia.[22] However, its usefulness in monitoring sedation levels remains controversial. Previous reports have attempted to correlate BIS values to clinical assessment to predict the depth of sedation-anesthesia.[10,23–25] Pollock et al. used BIS values and OAA/S scores during spinal anesthesia without sedation. In the present study, OAA/S was found to be a more sensitive tool for the assessment of sedation during spinal anesthesia compared with BIS.[26]

In the present study, BIS values varied depending on the specific sedative agent and the depth of sedation. It has recently been reported that BIS values are dependent on the variable EEG spectrums observed with specific sedative agents.[12] Rampil et al.[27] reported that BIS monitoring was insufficiently sensitive to assess the level of sedation during nitrous oxide administration. The reliability and applicability of BIS monitoring used to guide propofol sedation has previously been reported.[8] Furthermore, BIS values have been shown to correlate with the level of sedation induced by propofol and to accurately predict loss of consciousness.[4,28] Kasuya et al.[13] reported that calibration for BIS varied between dexmedetomidine and propofol in healthy volunteers, and that BIS values for sedation were lower with dexmedetomidine compared with propofol. In the present study, BIS values in the dexmedetomidine group with OAA/S 3 were lower compared with those in the propofol group, although the difference was not statistically significant.

Dexmedetomidine induces conscious and light sedation through mechanism that differs from that of other sedatives,[29,30] and was associated with lower BIS values at the same OAA/S score in previous reports.[4,31] During dexmedetomidine sedation, 85% of BIS values are 40 to 60 with OAA/S score 3, representing a level considered to be an arousable and shallow sedation status.[13] Our findings showed that dexmedetomidine presented significantly higher values than midazolam and propofol in OAA/S 1 and 2, and lower values in OAA/S 3 that were not significantly different.

Imprecise estimation of BIS values can affect their correlation with subjectively assessed sedation levels. As reported, underestimation[13] and overestimation[31] of sedation levels predicted by BIS were observed with propofol and dexmedetomidine at different levels of sedation. In addition, different EEG dynamics at the same sedation level might account for differences in BIS values via different mechanisms for each sedative.[27]

In the present study, BIS values accurately reflected the level of sedation during dexmedetomidine sedation. The OAA/S score required for adequate sedation was 3 and BIS values were lower with dexmedetomidine compared with propofol and midazolam, although the difference was not statistically significant. Further studies are necessary to evaluate whether BIS values accurately reflect the level of sedation with dexmedetomidine compared with the other sedatives, and whether these values can precisely reflect the level of sedation in general.

BIS monitoring is widely used during sedation with dexmedetomidine, propofol, and midazolam. Sedation induces agent-specific changes in EEG dynamics that can vary according to the depth of sedation. The utility of BIS monitoring in guiding continuous sedation during spinal anesthesia requires further evaluation using different sedative agents at variable levels of sedation. Therefore, further studies defining BIS standards during sedation are required to enable the application of BIS monitoring in clinical settings.

Our findings showed that BIS values were increased with midazolam compared with propofol and dexmedetomidine at OAA/S scores between 1 and 2. BIS values did not precisely reflect the level of sedation during deeper sedation using midazolam. Clinicians should therefore be aware that the level of sedation may be deeper than that reflected by BIS values. A limitation of the present study is that supplemental doses of propofol may have affected the level of sedation and subsequent BIS values, which may have been interpreted as excessive sedation. In the present study, one patient in the propofol group and four patients in the midazolam group were administrated supplemental doses of propofol. No supplemental dose was required in the dexmedetomidine group, and no patient required supplemental fentanyl administration.

Our findings do not support the reliability of BIS as a measure of sedation depth, and no standardized values that accurately reflect the depth of sedation with specific sedative agents were obtained. When determining the depth of sedation during spinal anesthesia, the characteristics of each sedative agent should be considered. Clinicians should assess the depth of sedation using a combination of BIS values and other objective sedation scales, and assessment should not rely solely on BIS values.

In summary, during deep sedation (OAA/S 1–2), BIS values in patients receiving midazolam were significantly higher than those receiving propofol and dexmedetomidine. Anesthesiologists using midazolam for sedation should use a combination of BIS values and objective sedation scores to evaluate the level of sedation during spinal anesthesia.

Acknowledgements

The statistical analysis of this study was supported by the Division of Biostatistics, Hallym Institute of Clinical Medicine, Hallym University Medical Center.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research was supported by Hallym University Research Fund (HURF-2018-13), and Reo-supply provided with BIS sensors.

ORCID iD

Yi Hwa Choi https://orcid.org/0000-0001-6055-3473

References

1. Chernik DA, Grillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale study with intravenous midazolam. *J Clin Psychopharmacol* 1990; 10: 244–251.
2. Hirota K, Kubota T, Ishihara H, et al. The effects of nitrous oxide of ketamine on the bispectral index and 95% spectral edge frequency during propofol-fentanyl anaesthesia. *Eur J Anaesthesiol* 1999; 16: 779–783.
3. Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 1998; 89: 980–1002.
4. Glass PS, Bloom M, Kearse L, et al. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology* 1997; 86: 836–847.
5. Liu J, Singh H and White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. *Anesth Analg* 1997; 84: 185–189.
6. Yi Y, Heo D, Son HJ, et al. Association between bispectral index and age and use of sedative drugs in high spinal anaesthesia. *J Int Med Res* 2013; 41: 378–385.
7. Liu J, Singh H and White PF. Electroencephalographic bispectral analysis predicts the depth of midazolam-induced sedation. *Anethesiology* 1996; 84: 64–69.
8. Sebel PS, Lang E, Rampil IJ, et al. A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. *Anesth Analg* 1997; 84: 891–899.
9. Leslie K, Sessler DI, Schroeder M, et al. Propofol blood concentration and the bispectral index predict suppression of learning during propofol/epidural anesthesia in volunteers. *Anesth Analg* 1995; 81: 1269–1274.
10. Ibrahim AE, Taraday JK and Kharasch ED. Bispectral index monitoring during sedation with sevoflurane, midazolam, and propofol. *Anesthesiology* 2001; 95: 1151–1159.
11. Brown CH, Azman AS, Gottschalk A, et al. Sedation depth during spinal anesthesia and survival in elderly patients undergoing hip fracture repair. *Anesth Analg* 2014; 118: 977–980.
12. Xi C, Sun S, Pan C, et al. Different effects of propofol and dexmedetomidine sedation on electroencephalogram patterns: wakefulness, moderate sedation, deep sedation and recovery. *PLoS One* 2018; 13: e0199120.
13. Kasuya Y, Govinda R, Rauch S, et al. The correlation between bispectral index and observational sedation scale in volunteers sedated with dexmedetomidineandpropofol. *Anesth Analg* 2009; 109: 1811–1815.
14. Hernandez-Gancedo C, Pestana D, Peria N, et al. Monitoring sedation in critically ill patients: bispectral index, Ramsay and observer scales. *Eur J Anaestehsiol* 2006; 23: 649–653.
15. Zheng J, Gao Y, Xu X, et al. Correlation of bispectral index and Richmond agitation sedation scale for evaluating sedation depth: a retrospective study. *J Thorac Dis* 2018; 10: 190–195.
16. DeLong ER, DeLong DM and Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. *Biometrics* 1988; 44: 837–845.
17. Kato T, Koitabashi T, Ouchi T, et al. The utility of bispectral index monitoring for sedated patients treated with low-dose remifentanil. *J Clin Monit Comput* 2012; 26: 459–463.
18. Bonhomme V and Hans P. Monitoring depth of anaesthesia: is it worth the effort? *Eur J Anaesthesiol* 2004: 21: 423–428.
19. Singh H. Bispectral index monitoring during propofol-induced sedation and anaesthesia. *Eur J Anaesthesiol* 1999, 16: 31–36.
20. Triltsch AE, Welte M, von Homeyer P, et al. Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study. *Crit Care Med* 2002; 30: 1007–1014.
21. Jo YY, Lee D, Jung WS, et al. Comparison of intravenous dexmedetomidine and midazolam for bispectral index-guided sedation

during spinal anesthesia. *Med Sci Monit* 2016; 4: 3544–3551.
22. Fahy BG and Chau D. The technology of processed electroencephalogram monitoring devices for assessment of depth of anesthesia. *Anesth Analg* 2018; 126: 111–117.
23. Katoh T, Bito H and Sata S. Influence of age on hypnotic requirement, bispectral index, and 95% spectral edge frequency associated with sedation induced by sevoflurane. *Anesthesiology* 2000; 92: 55–61.
24. Veselis RA, Reinsel RA, Wronski M, et al. EEG and memory effects of low-dose infusions of propofol. *Br J Anesth* 1992; 69: 246–254.
25. Kearse LA, Manberg P, Chamoun N, et al. Bispectral analysis of the electroencephalogram correlates with patient movement to skin incision during propofol/nitrous oxide anesthesia. *Anesthesiology* 1994; 81: 1365–1370.
26. Pollock JE, Neal JM, Liu SS, et al. Sedation during spinal anesthesia. *Anesthesiology* 2000; 93: 728–734.
27. Rampil IJ, Jin-Soo K, Lenhardt R, et al. Bispectral EEG index during nitrous oxide administration. *Anesthesiology* 1998; 89: 671–677.
28. Iselin-Chaves IA, El Moalem HE, Gan TJ, et al. Changes in the auditory evoked potentials and the bispectral index following propofol or propofol and alfentanil. *Anesthesiology* 2000; 92: 1300–1310.
29. Correa-Sales C, Rabin BC and Maze M. A hypnotic response to dexmedetomidine, an alpha 2 agonist, is mediated in the locus coeruleus in rats. *Anesthesiology* 1992; 76: 948–952.
30. Nacif-Coelho C, Correa-Sales C, Chang LL, et al. Perturbation of ion channel conductance alters the hypnotic response to the alpha 2-adrenergic agonist dexmedetomidine in the locus coeruleus of the rat. *Anesthesiology* 1994; 81: 1527–1534.
31. Frase GL and Riker RR. Bispectral index monitoring in the intensive care unit provides more signal than noise. *Pharmacotherapy* 2005; 25: 19s–27s.