

Usefulness of bispectral index and patient state index during sevoflurane anesthesia in children

A prospective observational study

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Abstract

Cortical electroencephalography-based devices are used to monitor the depth of anesthesia. In this study, we evaluated the values of bispectral index (BIS) and patient state index (PSI) during sevoflurane anesthesia in children. The ability/accuracy of BIS and PSI to predict the maintenance and recovery state of anesthesia was evaluated based on prediction probability (Pk) values and the secondary outcomes were agreement and correlation of 2 monitors.

Fifty children (3–12 years old) were enrolled and the patients received sevoflurane anesthesia with remifentanyl followed by propofol administration. Before the induction of anesthesia, BIS and PSI sensors were simultaneously placed on the forehead, and data were collected until the end of anesthesia. Maintenance state was defined as the period following intubation until the cessation of sevoflurane, while recovery state was defined as the period following the cessation of sevoflurane until awake. Pk, agreement or correlation of BIS and PSI in different anesthesia state were calculated.

Anesthesia reduced mean BIS and PSI values. Pk of BIS (95% confidential interval [CI]: 0.78–0.91) and PSI (95% CI: 0.82–0.91) for anesthesia were 0.85 and 0.87, respectively. Agreement was 0.79 for recovery state and 0.73 for maintenance state. Pk values were comparable for BIS and PSI.

Agreement between BIS and PSI measurements in the same state was relatively good. Therefore, these monitors are appropriate for monitoring for different state of anesthesia in pediatric population.

Abbreviations: BIS = bispectral index, EEG = electroencephalography, $E_t\text{CO}_2$ = end-tidal carbon dioxide, HR = heart rate, NIBP = noninvasive blood pressure, PACU = postanesthetic care unit, Pk = prediction probability, PSI = patient state index, SD = standard deviation, SpO_2 = peripheral oxygen saturation.

Keywords: bispectral index, children, depth of anesthesia, patient state index, prediction probability

1. Introduction

Cortical electroencephalography (EEG) is commonly used to monitor the cerebral effects of general anesthetics.^[1] The most popular commercial device which was developed using EEG data collected from adult volunteers might be bispectral index (BIS, version XP; Aspect Medical Systems, Natick, Mass Covidien, BIS-SX, USA) for monitoring anesthesia depth/sedation. Although BIS was developed with adult EEG data, many studies have utilized the BIS to monitor anesthesia depth in children.^[2] Now, we have several EEG-based monitors and indicators (e.g., Entropy,^[3] Narcotrend,^[4] cerebral state index [CSI],^[5] index of consciousness [IoC],^[6] qCON,^[7] A-line autoregression index [AAI],^[8] brain anesthesia response [BAR],^[9] and patient state index [PSI]^[10]) in clinical practice. Many studies comparing

the performance of these monitors have shown the comparable results between the monitors. The manufacturer of each monitor has presented the advantages or differences from other comparable monitors.

Among the aforementioned indicators, the PSI is derived from 4-channel EEG data from bilateral attachable sensors (SedLine, Masimo, Inc, Irvine, CA).^[11] This monitor is advantageous in that it is associated with no pain upon attachment to the forehead and has more channels to give more information than BIS monitors, which present the unilateral EEG data affected by general anesthesia. Although several studies have compared the effects of different monitor types in human patients such as BIS with PSI, Entropy, or AAI.^[12–14] However, many anesthesiologists have only experienced at least 2 or 3 monitors in the different operating rooms during daily practice separately according

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to the facilities of the operating theater. Therefore, it would give the information if there is an evidence of the exchangeability between the monitors because of the scalers or the values of the monitors might be different during the same anesthetic concentration.

In this prospective observational study, we evaluated the values of BIS and PSI during sevoflurane anesthesia with regard to classification of different anesthetic state in the same patient using prediction probability (Pk).

2. Methods

2.1. Study population

This prospective observational study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no. 1811-172-991) and registered at <http://register.clinicaltrials.gov> (NCT03792334). Each participant was given a verbal explanation and had the time to ask questions about the study protocol, and written informed consent was obtained from 1 parent or guardian. All procedures followed the principles outlined in the Declaration of Helsinki and its revisions.

A total of 54 patients (age range: 3–12 years) undergoing surgery under sevoflurane anesthesia were enrolled in tertiary educational hospital. Exclusion criteria were as follows: known cerebral dysfunction, plans to receive intravenous anesthesia, use of antiepileptic drugs, or admission to the postoperative intensive care unit.

All patients fasted in accordance with practice guidelines outlined by the American Society of Anesthesiologists. Recruited patients did not receive premedication. Intravenous route was placed in the ward in all the recruited patients. After arrival in the operating room, electrocardiogram (ECG), heart rate (HR), noninvasive blood pressure (NIBP) data were collected at 1-min intervals. Peripheral oxygen saturation (SpO_2), and E_TCO_2 (end-tidal carbon dioxide) were also monitored. Pediatric unilateral BIS and pediatric PSI sensors were simultaneously attached to the forehead and the site of BIS sensor attachment was randomly chosen. Preoxygenation was performed, following which anesthesia was induced with 2.5 mg/kg of propofol through intravenous route, which was already placed. Patients were manually ventilated with a mixture of 8 vol% sevoflurane and 100% oxygen after loss of consciousness. Administration of 0.6 mg/kg of rocuronium was followed by endotracheal intubation, which was performed after confirming full neuromuscular blockade.

Anesthesia was liberally maintained using 2% to 3% of inspiratory sevoflurane concentration and continuous infusion of remifentanyl (0.1–0.2 $\mu\text{g/kg/min}$) according to the conventional technique of the attending pediatric anesthesiologist with BIS monitor and hemodynamic changes. We discontinued sevoflurane administration after surgery, following which patients were extubated according to the extubation criteria^[15] and transferred to the postanesthetic care unit (PACU).

Maintenance state was defined as the period from intubation until just prior to sevoflurane cessation, while recovery state was defined as the period from the cessation of sevoflurane administration until extubation.

2.2. Study protocol

To obtain EEG data of optimal quality, the skin of the forehead was swabbed with alcohol, following which the 2 pediatric sensors were gently attached. The BIS sensor was applied closer to the eyebrows, whereas the PSI sensor was applied above the BIS sensor. Although the electrodes were applied in close proximity, the interference between the 2 monitoring systems is expected to be minimal because they use sophisticated artifact rejection algorithms and amplifiers with medical-grade isolation

transformers. The bar readings on the monitors indicating signal quality and electromyogram activity were monitored, as were the raw EEG tracings. BIS and PSI values corresponding to poor signal quality combined with increased electromyogram activity and EEG artifacts were excluded from data analysis.^[16] Measurements were obtained once sensor impedance had been checked and accepted by both the BIS and PSI monitors. Two sensors were attached from the beginning of anesthesia to the end of anesthesia. During the study period, all vital signs and parameters were monitored and recorded using a computer for subsequent analysis. Data were collected to the computer using vital-recorder program (<http://vitaldb.net/>) in 1 Hz. The collected data were reviewed by one of the investigators and removed the artifact manually, which was occurred by patient movement, electrocautery, or other causes.

2.3. Outcome measures

The primary outcome measurement was Pk. Pk values were calculated using Somers' d cross-tabulation statistic to evaluate the performance of the monitor.^[17,18] Pk values reflect the ability of an indicator to correctly identify different state of anesthesia (maintenance vs recovery state) without overlap. Pk = 1 indicates that the measure predicts the observed depth of anesthesia perfectly; Pk = 0.5 indicates that the predictive accuracy of the measure is no better than chance (50: 50); and Pk = 0 indicates that the measure has no predictive value.

Agreement and correlation of the 2 devices were regarded as secondary outcomes. Agreement between the 2 monitors was defined as the percentage of BIS or PSI values simultaneously categorizing the state of the patients for a given state of anesthesia. Correlation was defined as the relationship between BIS or PSI values and sevoflurane concentration.

2.4. Sample size

The study was designed to detect a change in the mean Pk value of 0.08, that is, 80% of the expected standard deviation (SD) of the Pk value of 0.2 according to the previous study.^[19] At a desired power of 0.8 and an error of 0.05, 51 patients are required and plus 3 additional patients to correct for a possible drop-out.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 23.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as the mean $\pm$ standard deviation for normally distributed continuous variables, as the median (IQR: 25–75%) for non-normally distributed continuous variables, and as counts and percentages for categorical variables. A $P \leq .05$ was considered statistically significant.

3. Results

As data were lost for 4 patients, we analyzed data for a total of 50 patients. The demographic and surgical characteristics of the included patients are shown in Table 1. In 22 patients, BIS and PSI sensors were applied before anesthesia induction to obtain values for the awake state, which was usually over 97 of BIS, while the remaining participants refused sensor application. Due to excessive artifacts, awake-state BIS and PSI values were obtained in 5 and 7 patients, respectively.

The median (IQR: 25–75%) inspiratory sevoflurane concentration in maintenance state was 2.5 (2.2–2.8) and that in recovery state was lower (1.1 [0.1–1.6], $P < .001$). The median (IQR: 25–75%) expiratory sevoflurane concentration in maintenance state was 2.25 (2.0–2.4) and that in recovery state was lower (1.1 [0.6–1.4], $P < .001$). The median (IQR: 25–75%)

Table 1**Demographic and surgical characteristics.****Patients (n = 50)**

M/F	40/10
Age (yrs)	9.7 ± 2.1
Body weight (kg)	44.2 ± 13.8
Operation type	
Orthopedic	27 (54%)
Urologic	22 (44%)
Plastic	1 (2%)
Surgery time (min)	104.3 ± 52.1
Anesthetic time (min)	143.7 ± 56.1

Values are mean ± SD, counts, or percentage.

BIS during maintenance state was lower than that in recovery state (48 [40–56] and 61 [57–67], $P < .001$). The median (IQR: 25–75%) PSI value was lower than that in recovery state (38 [28–45] and 52 [45–64]), $P < .001$). Notably, we observed significance differences in BIS/PSI values between maintenance state and recovery state of anesthesia. Although the BIS or PSI values in recovery state was relatively lower than expectation of usual awake state, the values were significantly higher than the maintenance state. We also compared individual Pk values for distinguishing maintenance state and recovery state in a sample of 50 patients.

The Pk value for BIS was 0.85 (95% CI: 0.78–0.91), while that for PSI was 0.87 (95% CI: 0.82–0.91), suggestive of comparable prediction ability. The sensitivity of BIS and PSI was 0.84 and 0.81, respectively. The specificity of BIS and PSI was 0.79 and 0.80, respectively.

Agreement values for BIS or PSI were 0.79 and 0.73 during maintenance state and recovery state, respectively.

Figure 1 shows the raw BIS and PSI values plotted against the inspired and expired sevoflurane concentration. An inverse

relationship was observed between BIS/PSI values and inspired/expired sevoflurane concentration. We also analyzed the correlation between BIS or PSI values and inspiratory/expiratory sevoflurane concentration during the maintenance state and recovery state. Pearson correlation analysis was done and correlation coefficient between BIS/PSI and inspiratory sevoflurane concentration in study period was $-0.52/-0.34$ (95% CI: -0.53 to 0.50 , $P < .001$)/(95% CI: -0.36 to 0.32 , $P < .001$), respectively. In addition, correlation coefficient between BIS/PSI and expiratory sevoflurane concentration was $-0.52/-0.33$ (95% CI: -0.53 to 0.50 , $P < .001$)/(95% CI: -0.35 to 0.31 , $P < .001$), respectively. However, intrasubjective correlation between BIS and PSI versus inspiratory or expiratory sevoflurane concentration was relatively high in the present study (0.73 in inspiratory sevoflurane concentration, 0.72 in expiratory sevoflurane concentration, respectively).

4. Discussion

Our results demonstrated that BIS and PSI could both distinguish the maintenance state and recovery state of anesthesia in children with high prediction probability, although the correlations of BIS or PSI values with sevoflurane concentration were relatively weak. In addition, this means these 2 monitors might be exchangeable in pediatric population.

This is the first research for comparison of BIS and SedLine values during sevoflurane anesthesia in pediatric population to distinguish the different depth of anesthesia as far as we know. The result of the study showed these 2 monitors might be exchangeable to monitor the depth of anesthesia in children. And SedLine could be useful in children during general anesthesia with a scientific evidence.

A previous study reported that BIS-based methods are not reliable for assessing the depth of sevoflurane anesthesia in children under 2 years of age.^[20] Additional research has revealed that

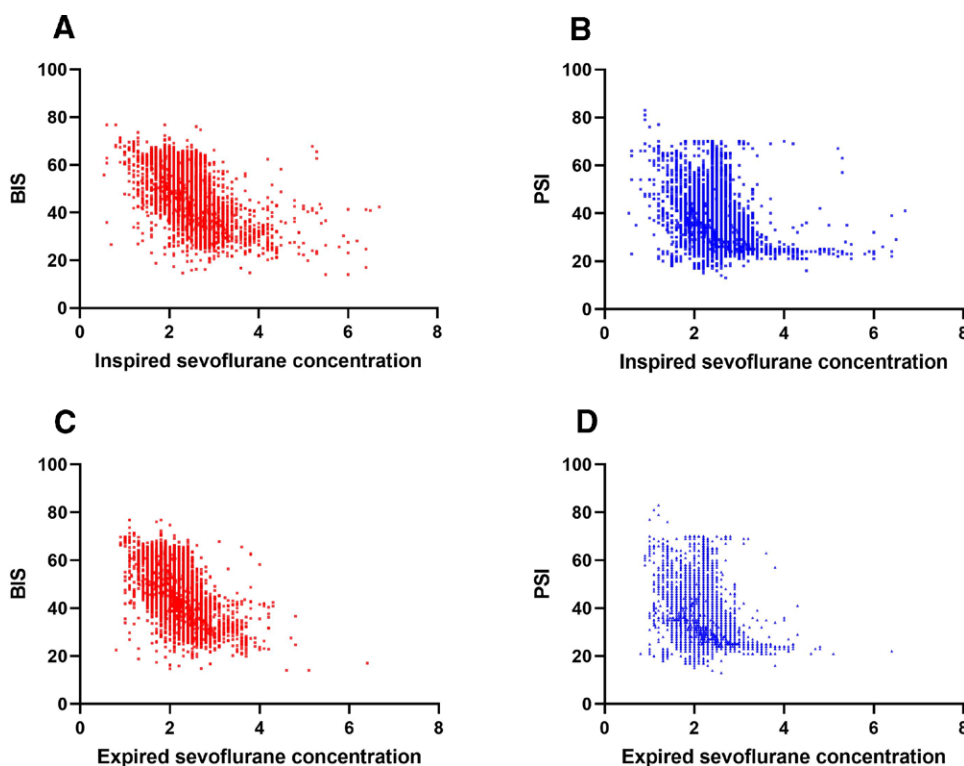


Figure 1. Plots of BIS and PSI against inspiratory sevoflurane concentration (A, B) or expiratory sevoflurane concentration (C, D) during the study period. Comparing to the inspiratory sevoflurane concentration, same values of BIS or PSI had a narrow expiratory sevoflurane concentration. BIS = bispectral index; PSI = patient state index.

the performance of BIS or entropy improves as age increases.^[21] In the present study, all patients were over 3 years of age (mean age: 9.7 years), allowing us to avoid this limitation. Moreover, it is difficult to apply 2 different sensors to the small foreheads of children under 3 years of age.

There is an inverse correlation between BIS values and end-tidal sevoflurane concentration in children, suggesting that EEG-based monitors can be applicable for monitoring anesthesia depth in this population. Our study also demonstrated an inverse correlation between sevoflurane concentration and BIS/PSI values shown in Figure 1. Relative to that for BIS values, the correlation between sevoflurane concentration and PSI values was poor in the present study. Although the reasons for this difference could not be determined with certainty, we also observed that fluctuations in PSI values tended to be greater than those in BIS values even at the maintenance state. The averaging time of BIS or PSI with the obtained EEG data were 15 seconds or 20 seconds, respectively, by manufacturer's default. Moreover, PSI values are shown after the manipulation of removal of artifact automatically. Therefore, it is not easy to evaluate the values directly. In addition, when the sensor was detached, PSI value started from 100 unlike BIS. Therefore, the values of PSI could give the bias to the result. This may explain why the correlation was weaker for PSI values than for BIS values.

Another study reported that elevated BIS values may indicate epileptoid patterns or EEG fast oscillations rather than an insufficient depth of hypnosis under high sevoflurane anesthesia. In this previous study, deep anesthesia was defined as a sevoflurane concentration over 4 vol%.^[22] In our study, the mean inspiratory/expiratory sevoflurane concentration during maintenance state was only 2.2/2.8 vol%, which is not considered high. Moreover, we did not include the induction period for analysis, which is common when using high concentrations of sevoflurane or bolus administration of propofol to avoid bias. Therefore, the mean inspiratory or expiratory sevoflurane concentrations observed in the present study were within the safe range to avoid the epileptoid pattern of EEG.

Several studies have compared the performance of different EEG-derived monitors and other monitors in the patients.^[5,13,23,24] Most of these studies reported comparable prediction probabilities for the different monitor types. In the present study, BIS and PSI yielded similar prediction probabilities for distinguishing the maintenance state from recovery state in children. This result is compatible with those of previous studies. In addition, basically, the present study was planned to evaluate the values of the 2 different devices, not to measure the absolute depth of anesthesia in children. Recent research has indicated that EEG parameters such as beta and delta band power are altered based on the depth of anesthesia in children and it would be helpful to develop the monitor with this finding.^[25] However, the algorithm of calculation of value of BIS was not unknown and basically developed with EEG of adults. Nevertheless, BIS might be the appropriate monitor for monitoring of depth of anesthesia for children with large number of researches to support this idea. Considering the usefulness of BIS monitor in children, PSI might be an alternative appropriate monitor for BIS from the result of this study because the agreement between BIS and PSI was relatively good in pediatric population in spite of different recommendation range of BIS or PSI for anesthesia.

In the present study, propofol administration was followed by inhalation of sevoflurane for the induction of anesthesia in pediatric population. Because BIS or PSI values may represent the mixed effects of propofol and sevoflurane during the induction period, we did not analyze the correlation between BIS/PSI values and sevoflurane concentration. If sevoflurane had been inhaled from the beginning, BIS or PSI values may have been correlated with the whole range of sevoflurane concentration. However, this study was designed to evaluate the BIS and PSI in the same patient, propofol effect was equal to both monitors.

At the same stable concentration of propofol, BIS values vary in children, relative to those observed in adults,^[26] and larger individual variations are observed during halothane or sevoflurane anesthesia in children.^[27] Despite these issues, several studies have utilized EEG-based methods to monitor the depth of anesthesia or hypnosis in children, as there is no gold standard for the pediatric population. The PSI is a different EEG-derived index that has been associated with a lack of pain upon attachment in patients. Although BIS and PSI are EEG-based indices, the algorithms used to manage the EEG data differ between the 2 monitors. Despite these differences, most previous studies have reported very good correlations between the 2 measures. Our results support the notion that BIS and PSI are comparable with regarding to agreement, correlation and prediction probability in children.

Remifentanyl was infused continuously during the study period with the rate of 0.1 to 0.2 µg/kg/min. Although the remifentanyl would affect the electroencephalogram, it was believed that the infusion of remifentanyl did not affect the result of the present study because we applied the BIS and PSI simultaneously in the same patient.

In this study, the correlation was relatively weak. We could explain this result by the maintenance state containing high inspiratory sevoflurane concentration before reaching the equilibrium of sevoflurane. If we refined the maintenance state, the correlation might be stronger. In addition, the BIS or PSI values were lower during the recovery state (median 62 vs 52) than the usual awake state because definition of recovery state was the period from the cessation of sevoflurane to extubation. Sevoflurane was not fully washed out during the recovery state and it would affect the BIS or PSI values. Moreover, the recruited patients were children who were the high-risk population of emergence delirium and it was exceedingly difficult to apply the BIS or PSI sensor after extubation in practice and we could not obtain the data.

5. Limitations

The present study possesses several limitations of note, including the arbitrary definition for the maintenance state and recovery state in clinical practice. However, this practice is common at our institution and reflects procedures applied in the pediatric population. Second, we used propofol and sevoflurane for the induction of anesthesia without EEG monitors. Therefore, we could not assess BIS and PSI values during the induction period. In addition, it was not easy to apply the BIS and PSI sensors in the alert state because due to fear among the included children. Third, we used the inspiratory sevoflurane concentration instead of expiratory sevoflurane concentration during recovery period. Usually, although most of the studies was applied end-expiratory concentration of inhalational anesthetics, it would take a long time to set the equilibrium of the anesthetics during recovery period and it is unethical to wait for the time to complete the study in children. Therefore, we used the inspiratory sevoflurane concentration to calculate Pk and it is more similar to the daily practice to support the result of the present study. Finally, the 2 sensors were applied simultaneously and one of sensors was inevitably applied in inappropriate position and this might become a bias of the result. Finally, BIS and PSI sensors were applied together and one of the sensors was inevitably attached in inappropriate position. However, the relationship between the sensors was same in the recruited patients and it did not give the bias for the result. Finally, the recruited patients were 51 in total and the actual power was reduced from 0.8 to 0.79 but the reduction was very small.

In conclusion, our findings demonstrate that BIS and PSI can both be used to monitor the maintenance state and recovery state in pediatric population over 3 years old, although the reference values for the 2 are different.

Author contributions

YEJ: This author helped in the design of the study, data acquisition, data analysis and interpretation, drafting of the article, statistical analysis and approval of the submitted version of the article.

EHK, MD: This author helped in the design of the study, data acquisition, data analysis and interpretation, and approval of the submitted version of the article.

JHL, MD, PhD: This author helped in the design of the study, data acquisition, and approval of the submitted version of the article.

JTK, MD, PhD: This author helped in the design of the study, data acquisition, and approval of the submitted version of the article.

HSK, MD, PhD: This author helped in the design of the study, data acquisition, data analysis and interpretation, statistical analysis, drafting of the article, and approval of the submitted version of the article.

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