Comparison of bispectral index and patient state index during sevoflurane anesthesia in children: a prospective observational study

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Abstract

Background: Cortical electroencephalography (EEG)-based devices are used to monitor the depth of anesthesia. In this study, we compared 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 two monitors.

Methods: Fifty children (3-12 years old) were enrolled and the patients received sevoflurane anesthesia with remifentanil. 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. The prediction probability (Pk), agreement or correlation of BIS and PSI in different anesthesia state were calculated.

Results: 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.

Conclusions: 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.

Trial Registry Number: Clinical Trials.gov NCT03792334.

Background

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[2] 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.[3] Now, we have several EEG-based monitors and indicators (e.g., Entropy,[4] Narcotrrend,[5] cerebral state index (CSI),[6] index of consciousness (IoC),[7] qCON,[8] A-line autoregression index (AAI),[9] brain anesthesia response (BAR)[10] and patient state index (PSI)[11]) 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).[12] 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.[13-15] However, many anesthesiologists have only experienced at least 2 or 3 monitors during daily practice and would like to confirm the exchangibility between the monitors.

In this prospective observational study, we compared the values of BIS and PSI during sevoflurane anesthesia with regard to classification of different anesthetic state in the same patient.

**Methods**

**Study population**

The present 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](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 one 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. 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), non-invasive blood pressure (NIBP) data were collected at 1-min intervals. Peripheral oxygen saturation (SpO₂), and E₇CO₂ 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 2-3% of inspiratory sevoflurane concentration and continuous infusion of remifentanil (0.1-0.2 ug/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 in fully awakened state and transferred to the postanaesthetic 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,
Study protocol

To obtain EEG data of optimal quality, the skin of the forehead was swabbed with alcohol, following which the two 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 two 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. 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/) The collected data was reviewed by one of the investigators and removed the artifact manually which was occurred by patient movement, electrocautery, or other causes.

Outcome measures

The primary outcome measurement was prediction probability (Pk). Pk values reflect the ability of an indicator to correctly identify different periods of anesthesia without overlap. A Pk value of 1.0 indicates that the parameter predicts the states correctly 100% of the time without overlap. A Pk value of 0.5 indicates that prediction accuracy is no better than chance alone. A Pk value <0.5 indicates an inverse relationship.[16] Individual Pk values were calculated using a specific PK program.

Agreement and correlation of the two devices were regarded as secondary outcomes. Agreement between the two 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.

Sample size[17]

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. At a desired power of 0.8 and an a of 0.05, 51 patients are required and plus 3 additional patients to correct for a possible drop-out.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 for Windows (SPSS Inc., Chicago, IL, USA). Data are expressed as the mean ± 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 ≤ 0.05 was considered statistically significant.
**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 < 0.001). The median [IQR 25-75%] expiratory sevoflurane concentration in maintenance state was 225[2.0-2.4] and that in recovery state was lower (1.1[0.6-1.4], P < 0.001). The median BIS during maintenance state was lower than that in recovery state (48[IQR 25-75%;40-56] and 61[57-67], P < 0.001). The median PSI value was lower than that in recovery state (38[IQR 25-75%;28-45] and 52[45-64]), P < 0.001). 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 (Table 2).

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's correlation analysis was done and correlation coefficient between BIS/PSI and inspiratory sevoflurane concentration in study period was -0.52/-0.34, respectively. In addition, correlation coefficient between BIS/PSI and expiratory sevoflurane concentration was -0.52/-0.33, respectively. However, intra-subjective 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).

**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.
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.[18] Additional research has revealed that the performance of BIS or entropy improves as age increases.[19] 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 two 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.[20] 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 sec or 20 sec, respectively by manufacturer’s default. Moreover, PSI values are shown after the manipulation of removal of artifact automatically. Therefore, it is not easy to compare 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%.[21] 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.[6, 14, 22, 23] 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 compare the values of the two 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.[24] 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 compare 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,[25] and larger individual variations are observed during halothane or sevoflurane anesthesia in children.[26] 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 two monitors. Despite these differences, most previous studies have reported very good correlations between the two measures. Our results support the notion that BIS and PSI are comparable with regarding to agreement, correlation and prediction probability in children.

Remifentanil was infused continuously during the study period with the rate of 0.1-0.2 ug/kg/min. Although the remifentanil would affect the electroencephalogram, it was believed that the infusion of remifentanil 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, table 2) 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.

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. Secondly, we used propofol and sevoflurane for the induction of anesthesia. 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. Thirdly, this study was performed in a single center. 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. Lastly, 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.

Conclusion

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 two are different.

Abbreviations


Declarations

Ethics approval and consent to participate

The present 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, Dec 28, 2018, https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0008KCO&selectaction=Edit&uid=U0000Y58&ts=6&cx=-22o4ut). 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 one parent or guardian. Verbal consent was obtained from patients under 7 years of age, while written informed consent was obtained from patients over 7 years of age. All procedures followed the principles outlined in the Declaration of Helsinki and its revisions.

Consent to publish

Non applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Competing interests
No conflicts to report from any of the authors.

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Author's contribution
SHJ: This author helped in the design of the study, data acquisition, data analysis and interpretation, drafting of the manuscript, and approval of the submitted version of the manuscript.

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

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 manuscript.

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

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

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

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References


### Tables

Table 1. Demographic and surgical characteristics
Table 2. Agreements of bispectral index and patient state index

<table>
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<tr>
<th>Anesthetic state</th>
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<td>Recovery state</td>
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<tr>
<td>Maintenance state</td>
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Figures
Figure 1

Plots of bispectral index (BIS) and patient state index (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.