Electroencephalographic Derivatives as a Tool for Predicting the Depth of Sedation and Anesthesia Induced by Sevoflurane

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Background: The electroencephalogram (EEG) has been evaluated as a tool for measuring depth of anesthesia, but the use of the EEG monitoring is still controversial. The current study was designed to evaluate the accuracy of three EEG parameters and anesthetic concentration for predicting depth of sedation and anesthesia during sevoflurane anesthesia.

Methods: One low and one high equilibrated concentration ranging from 0.2–1.8% were assigned randomly and administered consecutively to 69 patients. The bispectral index (BIS; version 3.2), 95% spectral edge frequency (SEF), and median power frequency (MPF) were obtained from a bipolar frontal-mastoid (Fp1-A1, Fp2-A2) montage using an EEG monitor. Sedation was assessed using the responsiveness portion of the observer’s assessment of alertness–sedation scale. In the second phase of the study, the patients who were scheduled to have skin incisions were observed for purposeful movement in response to skin incision at sevoflurane concentrations between 1.6% and 2.4%. The relation among BIS, 95% SEF, MPF, sevoflurane concentration, sedation score, and movement or no movement after skin incision, was determined. Prediction probability values for EEG parameters and sevoflurane concentration to predict depth of sedation and anesthesia were also calculated.

Results: The BIS and sevoflurane concentration correlated closely with the sedation score. Both 95% SEF and MPF changed significantly but biphasically with increasing sedation. The prediction probability values for BIS and sevoflurane concentration were 0.966 and 0.945, respectively, indicating a high predictive performance for depth of sedation. No EEG parameters predicted movement after skin incision better than chance alone.

Conclusions: Parameters derived from EEG, such as BIS, and 95% SEF are reliable guides to the depth of sedation, but not to the adequacy of anesthesia level for preventing movement during sevoflurane anesthesia. (Key words: Brain monitoring; bispectral index; depth of anesthesia; electroencephalogram; inhalational anesthetics.)

Electroencephalogram (EEG) patterns are known to change with the depth of sedation12 and general anesthesia level.4 Assessing the depth of anesthesia or sedation is difficult because the EEG pattern changes all seem to depend on the anesthetic used,12,3 and so the search for a drug-independent EEG parameter has been extensive. Quantitative EEG, such as 95% spectral edge frequency (95% SEF) and median power frequency (MPF), are examples. These EEG parameters may be useful monitors of anesthetic depth,6 although in other studies, the 95% SEF, MPF, and other EEG derivatives were found to be poor predictors of movement in response to skin incision, response to verbal command, and development of memory.7-8

Bispectral analysis of the EEG9,10 is a signal processing technique that has been proposed as a pharmacodynamic measure of anesthetic effects on the central nervous system. The bispectral analysis decomposes the EEG signal into its component sine waves using a Fourier transformation. A set of bispectral features is calculated by analyzing the phase relations between the component waves. These bispectral features are combined with other EEG features into a single measurement, the bispectral index (BIS), which is a numeric index ranging from 0 to 100.11 The BIS correlates well with sedation and is a good indicator of a patient’s response to stimulus,11-13 but it is not known whether BIS correlates with sevoflurane-induced sedation and anesthesia when sevoflurane is administered alone. The current study was designed to evaluate the efficacy of the BIS (version 3.2), quantitative EEG parameters (95% SEF and MPF) generated by an EEG monitor (model A1000; Aspect Medical Systems, Natick, MA) for predicting the depth of sedation and depth of anesthesia as defined by movement in response to skin incision during sevoflurane anesthesia.

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Table 1. Responsiveness Scores of the Modified Observer’s Assessment of Alertness/Sedation Scale (OAA/S)

<table>
<thead>
<tr>
<th>Responsiveness</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responds readily to name spoken in normal</td>
<td>5</td>
</tr>
<tr>
<td>tone</td>
<td>(alert)</td>
</tr>
<tr>
<td>Lethargic response to name spoken in normal</td>
<td>4</td>
</tr>
<tr>
<td>tone</td>
<td></td>
</tr>
<tr>
<td>Responds only after name is called loudly</td>
<td>3</td>
</tr>
<tr>
<td>and/or repeated</td>
<td></td>
</tr>
<tr>
<td>Responds only after mild prodding or shaking</td>
<td>2</td>
</tr>
<tr>
<td>Responds only after painful trapezius squee</td>
<td>1</td>
</tr>
<tr>
<td>z</td>
<td></td>
</tr>
<tr>
<td>Does not respond to painful trapezius squee</td>
<td>0</td>
</tr>
<tr>
<td>z</td>
<td></td>
</tr>
</tbody>
</table>

Materials and Methods

Participants

After approval was obtained from the ethics committee of our department, informed consent to participate in this study was acquired from all patients. The study group included 69 patients (29 men, 40 women), all classified as American Society of Anesthesiologists physical status I or II, who were scheduled for elective surgery. Patients ranged in age from 19–65 yr (44.7 ± 19.6 yr; mean ± SD). Exclusion criteria were a history of cardiac, pulmonary, or renal disease; a history of esophageal reflux or hiatus hernia; drug or alcohol abuse; significant obesity (body mass index >30); and contraindication for an inhalational induction. Patients fasted for at least 8 h before surgery and received no premedicant drugs.

Study Design

The effect of sevoflurane on the BIS, 95% SEF, MPF, and depth of sedation was evaluated at sub-minimum alveolar concentration end-tidal concentrations of 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1.0%, 1.1%, 1.2%, 1.3%, 1.4%, 1.6%, and 1.8%. One low concentration and one high concentration among these concentrations were first designed randomly into pairs. Low concentration was chosen from concentrations <1.2%, and high concentration was at least 0.5% higher than the low concentration. All patients were randomly given one of the paired sets. The low concentration was administered first, followed by the high concentration. After maintaining the end-tidal sevoflurane concentration for 15 min, the depth of sedation was assessed using the responsiveness component of the Observer’s Assessment of Alertness/Sedation (OAA/S) rating scale (table 1).14 This assessment procedure involves intro-

Electroencephalographic Monitoring

Electroencephalogram electrodes (ZipPrep; Aspect Medical Systems) were placed on the scalp in the following configuration: bipolar frontomastoid montage (Fp1-A1 and Fp2-A2; international 10–20 system of electrode placement). The impedance of each electrode was less than 2 kΩ. Electroencephalogram parameters including BIS (version 3.2), 95% SEF, and MPF were recorded continuously using an Aspect A1000 EEG monitor. The EEG data were analyzed continuously during successive 2-s data segments. The signals were bandpass filtered between 1 and 30 Hz. Bispectral and spectral smoothing rates were 10 and 15 s, respectively. Four artifact detection schemes (slow rate, suppression, motion, and high frequency) were enabled. Data averaged from the combined two leads are presented in this article, although similar results were obtained from the two channels separately. The BIS, 95% SEF, and MPF values were calculated by averaging the values during
the 45-s interval immediately before assessment. To minimize artifacts, patients were instructed not to open their eyes, talk, or move during the EEG recording before the sedation level was assessed.

Serial output files consisting of processed EEG parameters were collected on a personal computer. Gas concentration data, including sevoflurane, oxygen, and carbon dioxide obtained from an anesthetic gas analyzer, also were collected in a similar manner.

Anesthetic Techniques
All patients breathed through a face mask connected to a semiclosed anesthetic circuit. Fresh gas flow into the anesthetic circuit was 6 l/min. After an anesthesia face mask was fixed on the patients' face using a head strap, we confirmed that air leakage from the margin of the mask was minimal when positive or negative airway pressure was applied to the inside of the mask. To prevent contamination of end-tidal samples with inspired gas, dead space was augmented at the sampling port (between the mouthpiece and Y-piece) with tubing having an internal volume of 60 ml. For analysis, gas was drawn continuously at a flow rate of 200 ml/min from the sampling port, located between the face mask and the dead space. The concentrations of carbon dioxide, sevoflurane, and oxygen were measured continuously using an infrared anesthetic gas analyzer (Capnomac, Helsinki, Finland), which was calibrated before anesthesia for each patient using a standard gas mixture.

Anesthesia was induced with sevoflurane and oxygen, first during spontaneous ventilation and then during assisted ventilation, if required to keep tidal volume high enough to measure end-tidal anesthetic concentrations. The end-tidal carbon dioxide concentration was kept between 35 and 45 mmHg during the study period. The inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration constant at a predetermined value. After maintaining the end-tidal sevoflurane concentration for 15 min, depth of sedation was assessed. The assessments of depth of sedation were performed at one low and one high concentration, which were assigned before induction of anesthesia.

After these assessments, the inspired sevoflurane concentration was increased for tracheal intubation. Vecuronium (0.02 mg/kg) was administered for precurarization, and then paralysis was induced with 1.5 mg/kg succinylcholine, followed by tracheal intubation. Immediately after tracheal intubation, the inspired concentration of sevoflurane was adjusted to maintain the measured end-tidal concentration constant at a predetermined value. Thirteen of the 60 patients did not undergo a skin incision, and their EEG parameters were recorded after 25 min at constant end-tidal sevoflurane concentrations. In the 47 patients who had skin incision, gross purposeful movement in response to skin incision was tested after maintaining the end-tidal concentration constant for more than 15 min. Coughing, chewing, or swallowing was not considered movement. The EEG parameters including BIS, MPF, and 95% SEF were recorded before assessing the patients' movement in response to skin incision. Residual neuromuscular blockade was assessed by train-of-four stimulation of the ulnar nerve. We confirmed that the first twitch height at skin incision was not different from that recorded before administration of a muscle relaxant.

Statistical Analysis
Kruskal-Wallis analysis of variance was used to determine significant changes in each EEG parameter and in sevoflurane concentration. When $P < 0.05$, Bonferroni's correction to the Mann-Whitney rank sum test was used to distinguish differences between sedation score groups. The statistical data analysis was performed using Statview 4.02 (Abacus Concepts, Berkeley, CA).

Spearman's rank-order correlation analysis was performed to evaluate the relation between sedation scores and EEG parameters or sevoflurane concentration. The efficacy of sevoflurane concentration and EEG parameters to predict depth of sedation and movement in response to skin incision was evaluated using prediction probability (Pk), which compares the performance of indicators having different units of measurement. The mathematical basis of Pk was described by Smith et al.\textsuperscript{17} A Pk value of 1 means that the values of the predicting variable (e.g., anesthetic depth indicator) always correctly predict the value of the variable to be predicted (e.g., true observed anesthetic depth). A Pk value of 0.5 means that the values of the indicator predict no better than a 50–50 chance (flipping a fair coin). A Pk value was computed for all 138 sedation assessments combined. Similarly, Pk values for all 47 skin incision assessments combined were determined. The jackknife method was used to compute the standard error of the estimate, based on the assumption that the 138 assessments and the 47 skin incisions were independent. The predictive performance of sevoflurane concentration, BIS, 95% SEF, and MPF were compared. A paired-data jackknife analysis\textsuperscript{17} was used to determine
whether the Pk value for one indicator differed from that of another indicator. For multiple comparisons, we used Bonferroni’s correction to the paired-data jackknife analysis. Prediction probability was calculated using a custom spreadsheet macro, PKMACRO.17

We estimated median effective dose (ED$_{50}$) values of EEG parameters and sevoflurane concentration for preventing response to three non-noxious stimuli (verbal command in normal tone, loud or repeated verbal command, and verbal command after mild prodding or shaking) using a logistic regression analysis described by Waud.18 The ED$_{50}$ values for three non-noxious stimuli were compared by Waud’s technique.18 Similarly, ED$_{50}$ values for preventing movement after skin incision were estimated. The ED$_{95}$ value was calculated directly from the best-fitting logistic curve.

Probability values <0.05 were considered significant.

**Results**

With end-tidal sevoflurane concentration increasing from 0.2% to 1.4%, BIS values decreased almost linearly from 95.3 (median) to 45.5. Sevoflurane concentrations >1.4% produced a limited further reduction in BIS. The BIS values at 1.6% and 1.8% did not differ significantly between patients who underwent tracheal intubation and those who did not. The BIS showed no further decrease beyond 1.8% in intubated patients (fig. 1).

Quantitative EEG parameters (95% SEF and MPF) also varied with increasing end-tidal sevoflurane concentra-

![Fig. 1. Scatter diagram showing the relation among bispectral index, end-tidal sevoflurane concentration, and response to loud verbal command, or movement after skin incision. Open symbols denote either responders or movers, whereas filled symbols denote either nonresponders or nonmovers.](Image)

![Fig. 2. Scatter diagram showing the relation among 95% spectral edge frequency, end-tidal sevoflurane concentration, and response to loud verbal command, or movement after skin incision. Open symbols denote either responders or movers, whereas filled symbols denote either nonresponders or nonmovers.](Image)

![Fig. 3. Scatter diagram showing the relation among median power frequency, end-tidal sevoflurane concentration, and response to loud verbal command, or movement after skin incision. Open symbols denote either responders or movers, whereas filled symbols denote either nonresponders or nonmovers.](Image)
0.25% to 1.60% (figs. 4A and 4B). The BIS and sevoflurane concentration correlated closely with the sedation score. Spearman’s correlation coefficients between BIS, or sevoflurane concentration, and the sedation scores were 0.911 ($P < 0.0001$) and $-0.861$ ($P < 0.0001$), respectively. Both 95% SEF and MPF changed significantly but bilaterally with increasing sedation (figs. 4C and 4D). The Spearman’s correlation coefficients between 95% SEF or MPF and the sedation scores were 0.726 ($P < 0.0001$) and 0.298 ($P < 0.0005$), respectively. The Pk values (based on all 138 assessments) were 0.966 ± 0.008 (SEM) for sevoflurane concentration, 0.945 ± 0.009 for BIS, 0.812 ± 0.025 for 95% SEF, or 0.621 ± 0.038 for MPF. All indicators predicted sedation level significantly better than a 50–50 chance. No significant difference in Pk was observed between sevoflurane concentration and BIS. Prediction probabilities for BIS and sevoflurane concentration differed significantly from those for 95% SEF and MPF ($P < 0.0001$), and the Pk for 95% SEF was different from that for MPF ($P < 0.0001$).

Figures 5–7 show the relations between sevoflurane concentration, BIS, or 95% SEF and the probability of no response to three non-noxious stimuli. Table 2 lists the ED$_{50}$ and ED$_{95}$ values of sevoflurane, BIS, and 95% SEF for three non-noxious stimuli.

The Pk, which indicate the probability of correctly predicting if a patient will move in response to skin incision, was 0.902 ± 0.041 (SE) for sevoflurane concentration, 0.656 ± 0.084 for BIS, 0.571 ± 0.086 for 95% SEF, and 0.515 ± 0.088 for MPF. No EEG indicators

Fig. 5. Probability of no response to three kinds of non-noxious stimuli as a function of the end-tidal sevoflurane concentration. In the upper part of the figure, individual observations are presented. In the lower part, the values are median effective doses with 95% confidence intervals.
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predicted movement after skin incision better than chance alone, whereas sevoflurane concentration successfully predicted it. The Pk for sevoflurane concentration differed significantly from those for BIS, 95% SEF, and MPF. Because only sevoflurane concentration was shown to be a reliable indicator for predicting movement, the ED₉⁰ value of sevoflurane for skin incision (synonymous to minimum alveolar concentration) was determined to be 1.92 (95% confidence interval, 1.83–2.01%). The ED₉⁰ of sevoflurane was 2.26%. Figure 8 shows the relations between sevoflurane concentration and the probability that no movement after skin incision will occur. It was not possible to relate BIS, 95% SEF, or MPF and the probability of no movement using logistic regression analysis (fig. 9).

Discussion

The BIS closely correlated with sevoflurane concentration over the entire sedative range. At sevoflurane concentrations >1.4%, BIS did not decrease with increasing sevoflurane concentration. This means that the plateau of the sevoflurane concentration versus the BIS relation occurs before one reaches sevoflurane concentrations that completely suppress clinical responses, and sevoflurane produces a similar BIS at a range of anesthetizing concentrations, which are frequently used in clinical anesthesia.

Both BIS and sevoflurane concentration closely correlated with sedation score over a sedative range. The BIS was developed as a linear measure of sedation or hypnosis using a large database of EEGs. Anesthetic regimens included in developing the database included propofol, isoflurane, midazolam, and thiopental. During sedation induced by propofol, isoflurane, or midazolam, the BIS correlates linearly with sedation score. The current study extends these findings to sedation induced by sevoflurane. The OAA/S scale was chosen because it provides a good correlation with the clinical evaluation of sedation and has been tested prospectively. The correlation of BIS with sedation score did not differ significantly from that of sevoflurane concentration. This finding correlated with a recent study on the linear correlations between isoflurane concentrations or BIS and the OAA/S score. Ordinal values obtained using a responsiveness rating scale may not allow a perfect linear relation between the observed effect and the measure of anesthetic depth. To account for this uncertainty, Pk values, may provide a better measure to monitor performance, were proposed by Smith et al. The Pk value for BIS for sedation score was
Table 2. ED₉₀ and ED₉₅ Values of the Sevoflurane Concentration, 95% Spectral Edge Frequency (95% SEF), and Bispectral Index (BIS) for Three Types of Nonnoxious Stimuli: ED₉₀ (95% Confidence Interval)/ED₉₅

<table>
<thead>
<tr>
<th>Types of Nonnoxious Stimuli</th>
<th>Sevoflurane (95% CI)</th>
<th>BIS (95% CI)</th>
<th>95% SEF (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Command in normal tone</td>
<td>0.60 (0.56–0.63)/0.75</td>
<td>78.3 (76.1–80.5)/70.0</td>
<td>23.2 (21.5–25.1)/16.3</td>
</tr>
<tr>
<td>Loud and/or repeated verbal command</td>
<td>0.69 (0.65–0.74)/0.91</td>
<td>73.1 (70.9–75.3)/64.6</td>
<td>20.3 (19.1–21.4)/13.7</td>
</tr>
<tr>
<td>Loud repeated command after mild prodding</td>
<td>0.83 (0.75–0.87)/1.00</td>
<td>66.1 (63.8–68.3)/57.5</td>
<td>18.7 (17.5–19.9)/14.6</td>
</tr>
</tbody>
</table>

There were significant differences in ED₉₀ between the three types of nonnoxious stimuli, except between loud and/or repeated verbal command and tactile stimuli in 95% SEF (*).

0.945. The good correlation between BIS and depth of sedation, coupled with the excellent Pk value, indicates that BIS is a reliable guide to the depth of sedation. No significant difference in the Pk and the linear correlation coefficient was observed between sevoflurane concentration and BIS. These findings suggest that the utility of BIS to predict sedation level is similar to that provided by measuring the end-tidal sevoflurane concentration, when sevoflurane was administered alone. This finding corresponds with that of the previous study, indicating that the Pk value for isoflurane concentration was not significantly different from that for BIS in predicting whether patients were conscious or unconscious.

In the current study, a good correlation existed between 95% SEF and sedation score. This finding corresponded with results of previous studies. Other studies, however, showed that the 95% SEF was not a useful guide to depth of sedation. Because 95% SEF exhibits a biphasic response to increases in the sedation score, it is difficult to assess sedation level using it without other parameters. Because the Pk for 95% SEF was significantly different from that for BIS or sevoflurane concentration, the utility of the 95% SEF to predict sedation level is no greater than that provided by measuring the end-tidal concentration of anesthetic, when administering a single inhaled agent.

The lower Pk value for MPF indicates that MPF predicts sedation level no better that BIS and 95% SEF. In addition, MPF exhibited a biphasic response to increases in the sedation score. It seems difficult to assess depth of sedation using only MPF. Some researchers reported that MPF monitoring provides information about depth of sedation, and others claimed that MPF did not correlate with depth of sedation. Further studies are required to evaluate the use of MPF for assessing depth of sedation.

The BIS compared with the probability of no response to loud and/or repeated verbal command followed a

![Graph](image)

Fig. 8. Probability of no movement after skin incision as a function of the end-tidal sevoflurane concentration. In the upper part of the figure, individual observations are presented. In the lower part, the value is the median effective dose with the 95% confidence interval.

![Graph](image)

Fig. 9. Each symbol represents a patient. None of the bispectral index, 95% spectral edge frequency, or median frequency values predicted movement after incision.

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similar pattern, but the no-response probability significantly shifted to the left of the BIS when verbal commands were in a normal tone. The BIS responses to verbal commands after tactile stimuli shifted significantly further to the left (fig. 6). A similar pattern appeared with respect to the relations between sevoflurane concentration or 95% SEF and probability of no response to these verbal stimuli (figs. 5 and 7). These data suggest that a greater depth of sedation (i.e., lower BIS values and higher anesthetic concentrations) is required to prevent a response to a physical stimulus (i.e., shaking the patient) than to a verbal stimulus. The ED$_{50}$ of BIS for preventing response to a loud or repeated verbal command was 73.1 (95% CI, 70.9–75.3). During midazolam, propofol, and isoflurane anesthesia, a similar ED$_{50}$ of BIS was reported. These findings suggest that the ED$_{50}$ of BIS for preventing response to a verbal command may be independent of the anesthetic technique. In the present study, we found that the ED$_{50}$ of sevoflurane concentration was 0.60% (0.56–0.63%) for preventing a response to verbal commands in a normal tone, and 0.69% (0.65–0.74%) for loud or repeated verbal commands. These findings correspond to our previous minimal alveolar concentration$_{\text{awake}}$ studies. Regression analysis and the Pk statistic assumed independent data. Repeating the sedation score assessment twice in each patient, although economical, may result in an inpatient correlation that violates this assumption. In the absence of a comparable statistic with which to analyze these data, we have accepted, as have others, the potential error introduced into our results. Despite these problems, the derived functions appear to adequately describe our data.

No EEG parameters predicted movement after skin incision better than chance alone, whereas sevoflurane concentration successfully predicted it. In a previous study, 95% SEF and MPF did not predict movement after skin incision when isoflurane was administered as a single anesthetic agent. In contrast, when patients were anesthetized with sevoflurane in combination with alfentanil, a significant difference was found between 95% SEF for movers compared with nonmovers. The results of another study indicated that another version of BIS (version 1.1) can be used to predict patient movement in response to skin incision during isoflurane anesthesia. During propofol–nitrous oxide anesthesia, EEG parameters such as BIS, 95% SEF, and MPF predict movement as well as blood or effect-site concentration do. Further research is required to establish the utility of these EEG parameters for predicting depth of anesthesia as defined by movement in response to skin incision.

Some observers suggest that motor response to a noxious stimulus may be primarily mediated by subcortical structures including the spinal cord, at least in lower animals. Therefore, parameters derived from EEG, which do not reflect activity of the subcortical structures directly, may not be reliable for predicting responsiveness to noxious stimuli. In contrast, purposeful responsiveness to a verbal command apparently requires intact cortical functioning. Monitoring cortical function (EEG) thus may be useful to assess sedation level. Different endpoints (no response to a verbal command compared with no movement after skin incision) may be associated with different sites of anesthetic action.

Limitations of the Present Study

Because only two leads were used to monitor EEG, much of the possible EEG information was not obtained. Electroencephalographic effects differ significantly depending on the electrode positions; therefore, to truly describe EEG effects, about 20 electrodes are required. In addition, BIS, SEF, and MPF, although they provide some information, do not thoroughly describe all the EEG effects. The OAA/S scale can be scored subjectively, but the observer was not completely blinded to either the sevoflurane concentrations or the EEG parameters, which introduces a potential for interobserver bias into our results.

In conclusion, the BIS (version 3.2) was related linearly to sevoflurane concentration over a sedative range and closely correlated with depth of sedation in patients receiving sevoflurane for sedation. Of the EEG indicators evaluated in this study, BIS was the most accurate for predicting the depth of sedation. The results of this study indicate that when sevoflurane is administered alone, none of the EEG indicators, including BIS, was a reliable guide to the adequacy of anesthesia in preventing movement during sevoflurane anesthesia.

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