Comparison of bispectral index and phase lag entropy during general anesthesia

Sevoflurane or propofol anesthesia

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Abstract

**Background:** Phase-lag entropy (PLE) based on functional connectivity between different regions of the brain may be superior to conventional depth of anesthesia (DoA) methods for monitoring changes in consciousness. However, few studies have compared the PLE and bispectral index (BIS) methods for monitoring consciousness during clinical anesthesia, such as total intravenous anesthesia (TIVA) or anesthesia via inhalation. Therefore, we evaluated differences between the PLE and BIS methods in clinical anesthesia, including TIVA using propofol and anesthesia with sevoflurane.

**Methods:** The observational trial included 60 patients scheduled for elective surgery under general anesthesia. The BIS and PLE electrodes were placed together on the left temporal-frontal area of all patients. During anesthesia, anesthetic levels were adjusted using the BIS values, which are generally used to monitor the DoA; the level of anesthesia was maintained at between 40 and 60. BIS- and PLE-derived values were recorded continuously. Anesthetic events, the concentration of each anesthetic, and standard monitoring values were recorded. The patients included were divided into 2 groups, the TIVA and sevoflurane groups, with 30 patients in each. For the TIVA group, anesthesia was induced and maintained using propofol and remifentanil target-controlled infusion. For the sevoflurane group, anesthesia was induced using propofol and maintained using sevoflurane and remifentanil.

**Results:** From loss of consciousness until the anesthetic maintenance period, PLE values were higher than BIS values at several time points. During the recovery period, BIS values were higher than PLE values (all \( P < .001 \)). Spaghetti plots showed that there was more variation among the BIS values than among the PLE values.

**Conclusions:** For monitoring DoA during general anesthesia and surgery, PLE values vary less than BIS values; thus, PLE may be more reliable for monitoring changes in consciousness. However, further studies are needed to evaluate the clinical application of these methods in general anesthesia.

**Abbreviations:** BIS = bispectral index, DoA = depth of anesthesia, EEG = electroencephalography, EMG = electromyography, LOC = loss of consciousness, PLE = phase lag entropy, ROC = recovery of consciousness, TCI = target-controlled infusion, TIVA = total intravenous anesthesia, TOF = train of four.

**Keywords:** anesthesia, consciousness, monitoring

1. Introduction

Unconsciousness is the most important aspect of general anesthesia. An overdose of anesthetic can lead to various complications, whereas inadequate anesthesia can lead to intraoperative awareness. Both are major problems. There are commercially available devices for monitoring the depth of anesthesia (DoA) using electroencephalography (EEG), such as the bispectral index (BIS) monitor manufactured by Covidien Medical (Boulder, CO). However, there is no consensus definition of adequate unconsciousness under anesthesia and no standardized method of monitoring this. Therefore, reliable monitoring of DoA is still a clinical concern for anesthesiologists\textsuperscript{[1]}.
The BIS method is the most widely used validated means of monitoring DoA. In this method, an algorithm is used to calculate index values from frontal EEG channel derived information, such as a time domain (i.e., burst suppression and QUASI suppression), a frequency domain (i.e., relative beta ratio), and a bispectral domain (i.e., SynchFastSlow).\[21\] The BIS method decreases the risk of intraoperative awareness,\[2,3\] and increases the speed of patient recovery.\[14,15\] However, the effectiveness of using the BIS method has been questioned.\[4,5\] It has some limitations: it is affected by the electromyography (EMG) signal and may increase the risk of surgical artifact contamination due to the use of a single channel for EEG processing.\[6,7\] In addition, the smoothing time required for the algorithm is relatively long (10 seconds), and conventional DoA monitoring devices do not integrate information from different regions of the brain because they rely on the analysis of a spectrum from a single-channel EEG signal.\[8,9\]

Consciousness is closely linked to the temporal dynamics of a functional network configuration rather than the strength of static connectivity.\[10–12\] Furthermore, anesthesia-related unconsciousness is linked to a reduction in these brain patterns.\[10,13\] The phase lag entropy (PLE) method monitors DoA using the PLEM100 device manufactured by InBody (Seoul, Republic of Korea), which calculates differences in temporal connectivity patterns for the phase relationship between 2 frontal EEG signals.\[14,15\] Therefore, the PLE method should reflect levels of consciousness better than DoA methods conventionally used for clinical anesthesia, such as BIS values, because PLE measures functional connectivity, which is directly related to consciousness. The BIS and PLE methods both calculate index values ranging from 0 to 100 that represent particular stages of anesthesia (i.e., 80–100: awake; 60–80: sedation; 40–60: general anesthesia; <40: deep anesthesia).

Few studies have compared the PLE and BIS methods. Previous studies have reported a strong correlation between PLE measurements and consciousness level.\[14–16\] Other studies have shown a strong correlation between PLE and BIS measurements, despite major differences in the algorithms used by the 2 methods.\[16–18\] However, those studies evaluated the 2 methods during propofol-based intravenous anesthesia, and did not investigate anesthesia via inhalation. In this study, we evaluated the BIS and PLE methods throughout the duration of clinical general anesthesia. We investigated both total intravenous anestheisia (TIVA) using propofol and anesthesia using sevoflurane.

### 2. Methods

This prospective, observational, 2-group trial was approved by our hospital’s institutional ethics committee (SCHUH 2019–04–019) and was registered in the clinical trials registry (cris.nih.go.kr KCT 0004074). The trial was performed from July to November, 2019. All patients were provided with information about the trial, and all provided written informed consent. The primary endpoint was to compare the BIS and PLE methods throughout the process of clinical anesthesia. The secondary endpoints were to compare the BIS and PLE methods in 2 subgroups (1 subgroup was anesthetized using sevoflurane and the other subgroup had TIVA using propofol) and to assess the degree of variation in BIS and PLE values during the anesthetic period, as well as in the subgroups.

#### 2.1. Study participants and inclusion/exclusion criteria

The trial included 60 healthy patients aged 19 to 65 years old. These patients had American Society of Anesthesiologists physical status I or II and were scheduled for elective surgery under general anesthesia. The exclusion criteria were pregnancy, a body mass index >30 kg/m², disease of the liver or kidneys, a history of allergic reaction to any planned study medication, and impaired communication.

Patients were not stratified and a random number generator, based on Microsoft Excel software (ver. 2016; Microsoft Corp., Redmond, WA), was used to assign eligible patients to the TIVA group (TIVA group, n = 30) or sevoflurane group (Sevo group, n = 30) in a 1:1 ratio.

#### 2.2. General procedures

Patients were instructed how to express their level of consciousness on the day before surgery (e.g., respond to the investigator’s requests: “squeeze my hand” or “open your eyes”).

After arriving in the operating room, the investigators attached a BIS and a PLE sensor to each patient’s left temporal-frontal area. The BIS sensor was positioned above the PLE sensor, in accordance with the manufacturer’s instructions (Fig. 1). Next, we began noninvasive monitoring of blood pressure, electrocardiograph, oxygen saturation, and neuromuscular impulses. Thereafter, standard anesthesia was initiated. For the sevoflurane group, anesthesia was induced using 2 mg/kg propofol, 40 mg lidocaine, and 0.1 µg/kg/min remifentanil; anesthesia was maintained using sevoflurane and remifentanil (0–0.1 µg/kg/min). For the TIVA group, anesthesia was induced using an Orchestra pump (Fresenius Kabi, Brezins, France) by propofol target-controlled infusion (Schneider pharmacokinetic model of target-controlled infusion [TCI], Ce 4–6 µg/mL) and remifentanil TCI (Minto pharmacokinetic model of TCI, Ce 3 ng/mL); anesthesia was maintained using propofol TCI (Ce 2–5 µg/mL) and remifentanil TCI (Ce 0–3 ng/mL). BIS values were used to adjust anesthetic levels, and a level of 40 to 60 was maintained throughout anesthesia, whereas PLE values remained hidden. Remifentanil infusion was adjusted for surgical analgesia in both groups, based on vital and clinical signs.

After confirming loss of consciousness (LOC), 0.6 mg/kg rocuronium was given for tracheal intubation and surgery. All patients

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**Figure 1.** Sensor placement. (a) The PLE electrode array consisted of electrodes positioned at approximately FP1 (L1), FP2 (R1), AF5 (L2), and AF6 (R2). The ground electrode was positioned at Fpz (G), and the reference electrode was positioned at T3 on the temporal area (T). (b) The 2 sensors were positioned on the left temporal-frontal area with the BIS sensor placed above the PLE sensor. BIS = bispectral index, PLE = phase lag entropy.
were intubated after the train of four (TOF) count reached 0, and the lungs were ventilated mechanically with 50% oxygen in air. The respiratory rate was adjusted to maintain a tidal volume of 6 to 8 mL/kg and an end-tidal CO2 partial pressure of 30 to 40 mm Hg during anesthesia. When the TOF count reached 1 to 2, 10 mg rocuronium was given in incremental doses.

When skin closure began, 50 µg intravenous fentanyl was given and remifentanil infusion was stopped. After surgery, administration of anesthetics ceased and muscle relaxation was recovered by administering pyridostigmine and glycopyrrolate simultaneously. Extubation was performed when spontaneous breathing was observed and the TOF had reached 90%. Each patient was confirmed as having recovered consciousness, and 1 minute later the PLE and BIS sensors were removed and the patient was transferred to the post-anesthesia care unit.

2.3. Measurements
Preoperatively, demographic characteristics were recorded, including age, sex, weight, height, body mass index, American Society of Anesthesiologists physical status classification, and type of surgery. Throughout the anesthetic procedure, BIS-derived values (i.e., BIS values, EMG values from the BIS sensor and the BIS signal quality index) and PLE-derived values (i.e., PLE values, EMG values from the PLE sensor, the PLE signal quality index, and the raw EEG data from the PLE sensor) were recorded every 1 and 4 seconds, respectively. The recorded values were acquired from the PLE and BIS devices using a USB memory card. The PLE EEG bands for 4-second epoch data without overlap, and slow frequency (0.1–1 Hz) and gamma (30–45 Hz) bands for 8-second epoch data with 50% overlap, respectively, as described in equation 1 and 2. PLE1 reflects light hypnotic state, while PLE2, surgical hypnotic state. BSR includes 2 types of burst-suppression detection, such as the portions of isoelectric EEG and/or very low power frequency, for 60 seconds. Finally, PLE is calculated by combining PLE1, PLE2, and BSR with appropriate weights, which is linearly scaled to the range of 0 to 100. The ground electrode was at position Fpz, and the reference electrode was at position T3 on the temporal area (T) of the face (Fig. 1). Electrode impedance was <7 kΩ for each channel.

2.4. Electroencephalographic and PLE analysis
The electroencephalogram was continuously recorded at frontal (AF3, AF4) and prefrontal (FP1, FP2) montages with a preamplifier bandwidth of 0.5 to 45 Hz and sampling frequency (f) of 128 Hz (PLEM100, Inbody Co., Ltd, Seoul, Republic of Korea; Fig. 1). PLE between 2 EEG signals from frontal and prefrontal montages (AF3-FP1, AF3-FP2, AF4-FP1, AF4-FP2) was calculated, as proposed by Lee et al (Matlab 2017b, Mathworks Inc., Co., Ltd, Natick).[15] Direct current offset was performed by subtracting the average amplitude of every 4-second epoch data. Eye blink and high amplitude (>75 µV) artifacts were removed from the EEG signals.[16] The temporal phase difference between 2 EEG signals (Δt, t = 1, 2, ..., N) in the pre-processed data were binarized, where N is the number of data points sampled from 4 or 8-second epoch data.

The vector, Φt, representing the temporal pattern of the phase relationship between 2 EEG signals was given by

Φt = {Δt1, Δt2, ..., Δtm−1}, t = 1, 2, ..., N \times (m - 1) - τ

where τ represents time lag with a resolution of 1/f. The symbol m is the number of dimensions for extracting the temporal pattern of the phase relationship. If first signal is phase leading the second signal, temporal phase difference is positive, and Δt = 1. When first signal is phase lagging the second signal, temporal difference becomes negative, and Δt = 0. For example, with m = 3, 2m patterns of Φt can be generated: {0, 0, 0, 0, 0, 1, 0, 1, 0, 1, 0, 0, 0}, {1, 0, 1, 1, 1, 0, 1}.

PLE was calculated by applying the standard Shannon entropy formula to the distribution of the phase patterns.

\[ PLE = \frac{-\sum_{j=1}^{2^m} p_j \log_2 p_j}{\log_2 (2^m)} \]

\[ p_j = \frac{\text{count of } j\text{th pattern}}{N}, 0 < p_j < 1 \]

where \( p_j \) is the probability of the \( j \)th pattern in a given epoch. PLE is comprised of 3 sub-parameters, that is, PLE1 (m = 3), PLE2 (m = 5), and burst-suppression ratio (BSR). PLE1 and PLE2 are calculated in alpha (8–13 Hz) and beta (13–30 Hz) bands for 4-second epoch data without overlap, and slow frequency (0.1–1 Hz) and gamma (30–45 Hz) bands for 8-second epoch data with 50% overlap, respectively, as described in equation 1 and 2. PLE1 reflects light hypnotic state, while PLE2, surgical hypnotic state. BSR includes 2 types of burst-suppression detection, such as the portions of isoelectric EEG and/or very low power frequency, for 60 seconds. Finally, PLE is calculated by combining PLE1, PLE2, and BSR with appropriate weights, which is linearly scaled to the range of 0 to 100. The ground electrode was at position Fpz, and the reference electrode was at position T3 on the temporal area (T) of the face (Fig. 1). Electrode impedance was <7 kΩ for each channel.

2.5. Statistical analyses
The sample size for this study was not based on a power analysis because we did not compare parallel groups. In a previous study, 58 patients were sufficient to reveal differences between 2 DoA-monitoring methods, BIS and entropy.[20] We enrolled 60 patients (i.e., 30 patients in each of 2 groups), to accommodate a drop-out rate of up to 3%.

Statistical analyses were performed using SPSS software version 26 for Windows (IBM Corporation, Armonk, NY). The 2 groups were compared using Student’s t-test or the Mann-Whitney rank sum test for continuous data after checking for normality using the Kolmogorov–Smirnov test. Categorical data were evaluated using chi-square analysis or Fisher’s exact test.

We selected time points at which to compare PLE and BIS values based on the smoothing times of the algorithms (i.e., 4 second for PLEM and 10 second for BIS). To analyze the peri-LOC period, we selected the time of LOC and 30 and 60 seconds thereafter. To analyze the peri-ROC period, we selected the time of ROC and 30 and 60 seconds before and after consciousness was recovered. Other events were analyzed at the time of the event, as well as at 60 seconds thereafter. Paired PLE and BIS values at each point during anesthesia were compared using the Wilcoxon signed-rank sum test. All data are reported as means ± standard deviation or medians with Q2 and Q4. Categorical data are reported as frequencies and percentages. A P value <.05 was considered statistically significant.

3. Results
In total, 68 patients were screened. Five patients were excluded because they did not meet the inclusion criteria and 3 patients refused to participate. The remaining 60 patients were enrolled in the study and separated randomly into a sevoflurane group (Sevo group, n = 30) and a TIVA group (n = 30). All PLE data
from 1 patient in the TIVA group were corrupted. The data from the remaining 59 patients were analyzed (Fig. 2).

The baseline characteristics of the patients, the types of surgery, and the durations of anesthesia in the 2 groups were similar. The duration of induction (i.e., from anesthetic administration to LOC) was longer in the TIVA group ($P < .001$), whereas the duration of emergence (i.e., from stopping anesthetic administration to ROC) was longer in the Sevo group ($P = .002$). No patient reported awareness or recall (Table 1).

At baseline, before drug administration, BIS values were higher than PLE values, and this difference was statistically significant in the entire patient population ($P = .013$) and in the Sevo group ($P = .007$), but not in the TIVA group. Between LOC and the anesthetic maintenance period, PLE values were higher than BIS values at several time points. During the recovery period, BIS values were higher than PLE values in both groups (all $P < .001$; Fig. 3, Table 2).

PLE and BIS values were recorded every 5 minutes after LOC and displayed on spaghetti plots. These showed that there was more variation in BIS values than in PLE values in the entire patient population and in both groups (Fig. 4).

The group median spectrograms recorded for the maintenance and emergence periods showed the characteristics typical of sevoflurane and TIVA anesthesia.[21] For sevoflurane anesthesia, the spectrogram for the maintenance period showed alpha, theta, and slow-delta oscillations. For TIVA, the spectrogram for the maintenance period showed alpha and slow-delta oscillations. For both groups, the spectrograms for the emergence period showed that the alpha oscillations dissipated and were replaced by high frequency beta and gamma oscillations. However, the emergence-period spectrograms of the 2 groups differed. In the Sevo group, the median spectrogram for 4 minutes after the end of anesthetic administration showed that alpha and theta oscillations dissipated, whereas in the TIVA group the alpha oscillations did not dissipate. From 4 minutes before ROC, the median spectrograms showed alpha dissipation and beta replacement in both groups (Fig. 5).

4. Discussion

The PLE method, which quantifies the diversity of brain patterns using the phase relationship between 2 EEG signal channels (i.e., prefrontal and frontal), provides less variable index values during general anesthesia than does the BIS method. BIS values were higher than PLE values during the peri-ROC period, whereas PLE values were higher than BIS values at several time points during the anesthesia period, particularly during sevoflurane anesthesia.

Reliable monitors exhibit minimal inter-patient and baseline variability. The interquartile ranges and spaghetti plots in our study show that the PLE method was associated with less variability than was the BIS method. In addition, in a previous study,[14] the coefficients of variation for the PLE and BIS methods at 3 minutes before propofol administration were 3.3 and 5.7, respectively, indicating that the BIS method exhibits greater baseline variability. This may be due to the effects of several stimuli. Although the BIS method rejects artificial signals from epochs and rejected data can be replaced by interpolation, some stimuli that can affect several EEG domains (e.g., physical, mechanical, or pharmacological stimuli during surgery such as pain, electrical stimuli, and the use of opioids) can influence BIS values.[6–8,22] This can lead to inappropriate titration of anesthetics during anesthesia. In addition, remifentanil administration may affect the frequency content of BIS values, and may decrease their accuracy.[19] On the other hand, the PLE method quantifies the diversity of patterns using the phase relationship between 2 EEG signal channels without using other domains, such as frequency.[15] One recent study found differences between PLE and BIS values during nerve integrity monitoring, although no aberrant BIS or PLE values were observed.[18]

BIS values were higher than PLE values during the baseline and peri-ROC periods. Shin et al.[23] also reported that BIS values were higher than PLE values during the peri-ROC period. However, Seo et al.[18] reported that PLE values were higher than BIS values after full recovery from anesthesia and were similar to waking

![Figure 2. CONSORT diagram.](image-url)
baseline values. The differences from our results arose because we recorded data until 60 seconds after ROC, unlike Seo et al, who collected data until full recovery. However, they too reported that BIS values increased more rapidly during the early recovery period than did PLE values. The higher BIS values during peri-ROC periods may have been due to EMG contamination of the BIS index. Previous studies have reported effects of EMG or neuromuscular block on BIS index values. Dahaba et al reported

| Baseline variables                          | Sevo group (n = 30) | TIVA group (n = 29) | P    |
|--------------------------------------------|---------------------|---------------------|------|
| Age (yrs)                                  | 44.7 ± 11.67        | 43.0 ± 12.09        | .585 |
| Sex (n [males/females])                    | 5/25                | 4/25                | 1.000|
| Height (cm)                                | 161.60 ± 8.046      | 162.24 ± 6.174      | .733 |
| Weight (kg)                                | 59.36 ± 11.13       | 63.64 ± 10.54       | .164 |
| BMI (kg m⁻²)                               | 22.62 ± 3.08        | 23.95 ± 2.82        | .089 |
| ASA-PS (n I/II)                             | 24/6                | 21/8                | .493 |
| Surgery type (n)                           | Lap. gynecologic surgery 21 | 21 | .838 |
| lap. cholecystectomy                        | 9                   | 8                   |      |
| Anesthesia duration (min)                  | 128.13 ± 67.09      | 108.38 ± 34.81      | .161 |
| Induction duration (min)                   | 0.7 (0.53, 0.83)    | 1.6 (0.85, 3.48)    | <.001|
| Emergence duration (min)                   | 7.7 (6.02, 8.90)    | 4.8 (4.08, 7.00)    | .002 |

Values are presented as numbers for categorical data and means ± standard deviations or medians (IQR, 3Q), as appropriate, for continuous data. Anesthesia duration was the time between anesthetic administration and ROC. Induction duration was the time between anesthetic administration and LOC. Emergence duration was the time between stopping anesthetic administration and ROC. ASA-PS = American Society of Anesthesiologists physical status, BMI = body mass index, lap. = laparoscopic, LOC = loss of consciousness, ROC = recovery of consciousness.
higher BIS values for patients with a high-EMG signal of 35 dB or more during neuromuscular recovery. We suggest that EMG signals may affect BIS values during emergence. Unlike 1-channel indexes, such as BIS, PLE index values are calculated from 2 channels. Therefore, eye movements and EMG signals, which can occur simultaneously at different locations, may cancel each other out. However, we found no correlation between BIS-PLE values and EMG indexes during the baseline and recovery periods in this study, possibly because the BIS- and PLE-EMG values were considerably greater than 35 dB, and our study lacked the power to evaluate any correlation between them. Further evaluations of the effects of EMG signals on BIS-PLE index values and any variation due to the method of anesthesia are needed.

We showed that PLE index values were higher than BIS index values during the peri-LOC and anesthetic maintenance periods. This may have been due to the effects of the use of a neuromuscular blocking agent on BIS values, because a neuromuscular blocking agent was used to keep the TOF count below 2 during anesthesia in our study. In a previous study, fully conscious healthy volunteers who were administered muscle relaxants exhibited BIS values within the anesthesia range. However, PLE values were considerably higher than BIS values during sevoflurane anesthesia but not during TIVA. The large delta wave observed during anesthetic induction and the theta wave that is characteristic of anesthesia via inhalation may explain the differences in results between different types of anesthetics.

The PLE index represents the diversity of patterns based on the phase relationship between 2 EEG signal channels, excluding other domains such as frequency. Our median spectrogram results, based on EEG signals acquired using the PLE method, were consistent with patterns obtained for specific methods of anesthesia. During the recovery period, there were significant differences between the TIVA and sevoflurane anesthesia spectrograms. In the Sevo group, the alpha and theta waves decreased and the beta wave increased in both groups, resulting in sudden ROC. These differences in the spectrograms of the different types of anesthesia may be linked to the shorter recovery times observed in the TIVA group. In agreement with previous studies, the duration from discontinuation of anesthetic medication to ROC in this study was shorter in the TIVA group than in the Sevo group. These observations may also be due to differences in the anesthetic pharmacology of the inhaled anesthetics and propofol. However, further evaluation of the differences observed during recovery from anesthesia is needed.

This study had some limitations. First, the BIS and PLE electrodes were placed at slightly different locations on the forehead. This was because the electrodes used for the 2 methods had to function simultaneously. Any frowning or eye movement during recovery could have increased PLE values because the PLE electrode was positioned lower than the BIS electrode. However, in this study, PLE values were lower than BIS values during recovery. Therefore, any effects of frowning were probably insignificant. Second, the PLE and BIS values that we recorded at the same time point were not values for the same time point, due to the difference in smoothing times (4 seconds for PLE vs 10 seconds for BIS). Third, this study was unable to isolate the effects of EMG or other surgical stimuli on PLE or BIS values. The study could only show that BIS values were more diverse than PLE values across the entire period of anesthesia. Further studies will be necessary to determine how an EMG signal or other surgical stimuli may alter PLE or BIS values. Fourth, our investigation of anesthesia via inhalation was limited to using sevoflurane and our sample size was small. However, our results show that PLE values reliably reflected levels of consciousness during anesthesia via inhalation. Further studies with larger and more heterogeneous populations are needed to confirm that the PLE method can be used reliably with other anesthetics.

In conclusion, PLE shows less variation than BIS as a method for monitoring DoA. PLE is probably a reliable indicator of DoA for patients receiving TIVA or sevoflurane anesthesia. However, further studies are needed to evaluate the clinical meaning of these results for general anesthesia.

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**Table 2**

Comparison of BIS and PLE P values using the Wilcoxon signed-rank sum test.

| Time            | Total | Sevo group | TIVA group |
|-----------------|-------|------------|------------|
| Baseline        | 0.013 | 0.007      | 0.480      |
| LOC             | 0.133 | 0.539      | 0.103      |
| LOC + 30 s      | <0.001| <0.001     | 0.480      |
| LOC + 60 s      | 0.004 | <0.001     | 0.393      |
| Intubation      | 0.132 | 0.007      | 0.517      |
| Intubation + 60 s| 0.025 | <0.001     | 0.421      |
| Incision        | <0.001| <0.001     | <0.001     |
| Incision + 60 s | 0.007 | 0.478      | 0.002      |
| Fentanyl        | 0.060 | 0.104      | 0.330      |
| Fentanyl + 60 s | 0.009 | 0.009      | 0.222      |
| Anesthetic stop | 0.006 | 0.036      | 0.079      |
| Anesthetic stop + 60 s | 0.249 | 0.673      | 0.284      |
| ROC–60 s        | <0.001| <0.001     | <0.001     |
| ROC–30 s        | <0.001| <0.001     | <0.001     |
| ROC             | <0.001| <0.001     | <0.001     |
| ROC + 30 s      | <0.001| <0.001     | <0.001     |
| ROC + 60 s      | <0.001| <0.001     | <0.001     |

PLE and BIS paired values for each point in anesthesia were compared using the Wilcoxon signed-rank sum test. LOC was defined as loss of response to verbal questioning and ROC was defined as the first meaningful response to verbal questioning. Computed data (SQI < 40) were excluded. The smoothing time for the algorithms was 4 s for PLE and 10 s for BIS. LOC was evaluated at the moment consciousness was lost, as well as 30 s and 60 s thereafter. ROC was evaluated 30 s and 60 s both before and after consciousness was recovered. Other events were also evaluated at 60 s after the event. BIS = bispectral index, LOC = loss of consciousness, PLE = phase lag entropy, ROC = recovery of consciousness, SQI = signal quality index, TIVA = total intravenous anesthesia.
Figure 4. Variation in PLE and BIS values shown on spaghetti plots. PLE and BIS values were recorded every 5 min from LOC. LOC was defined as loss of response to verbal questioning and ROC was defined as the first meaningful response to verbal questioning. Two patients in the Sevo group and 1 patient in the TIVA group had corrupted initial data (SQI < 40). These corrupted data were excluded. (a) BIS values in all patients (n = 56); (b) PLE values in all patients (n = 56); (c) BIS values in the Sevo group (n = 28); (d) PLE values in the Sevo group (n = 28); (e) BIS values in the TIVA group (n = 28); (f) PLE values in the TIVA group (n = 28). BIS = bispectral index, LOC = loss of consciousness, PLE = phase lag entropy, ROC = recovery of consciousness, SQI = signal quality index.

Figure 5. Spectrograms recorded during the anesthesia maintenance and ROC periods. Spectral comparison of the groups recorded at the left frontal channel (AF5). (a) Median spectrogram for the Sevo group during the maintenance period; (b) Median spectrogram for the Sevo group 4 min after stopping anesthetic administration; (c) Median spectrogram for the TIVA group from 4 min before ROC to ROC; (d) Median spectrogram for the TIVA group during the maintenance period; (e) Median spectrogram for the TIVA group 4 min after stopping anesthetic administration; (f) Median spectrogram for the TIVA group 4 min before ROC to ROC. ROC = recovery of consciousness, TIVA = total intravenous anesthesia.
PLEM-ES 100 electrode. However, this support did not influence the results of the study. We are grateful to K-S Kim (InBody, Co., Ltd.) for assistance with the spectral and PLE data analyses.

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