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Original Contribution

Comparison of the performance of phase lag entropy and bispectral index for monitoring the depth of sedation under dexmedetomidine sedation: A prospective, observational, and non-inferiority trial

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ABSTRACT

Study objective: Although the performance of phase lag entropy (PLE), a new depth-of-sedation monitor based on the diversity of temporal patterns in the phase relationships in electroencephalogram (EEG) data, during propofol sedation has been proven through several studies, since different sedatives have different effects on EEG, we aimed to evaluate the performance of the PLE in comparison with the bispectral index (BIS) during dexmedetomidine sedation.
Design: A prospective, observational, and non-inferiority trial.
Setting: Tertiary university hospital operating room.
Patients: Forty-two patients aged 20–80 years who were scheduled to undergo elective surgery under spinal anesthesia and had American Society of Anesthesiologists (ASA) physical status I to III were enrolled in this study.
Interventions: Dexmedetomidine was administered with a loading dose of 0.5–1 μg/kg for 10 min, followed by a maintenance dose of 0.3–0.6 μg/kg/h.
Measurements: The depth of sedation was assessed using the modified observer's assessment of alertness/sedation (MOAA/S) scale; the data for PLE and BIS were collected; and vital signs, including blood pressure, heart rate, EKG, and pulse oximetry, were evaluated.
Main results: 215,082 data points for the MOAA/S score and PLE and BIS values were analyzed. The baseline variabilities of PLE and BIS were 4.53% and 7.02%, respectively. The Spearman correlation coefficients of the MOAA/S score with PLE and BIS were 0.599 and 0.566, respectively. The prediction probabilities of the MOAA/S score with PLE and BIS were 0.647 and 0.636, respectively. When the MOAA/S score was 3 points, the mean (SD) values of PLE and BIS were 68.35 (15.68) and 75.85 (9.81), respectively, However, the mean (SD) values of PLE and BIS for an MOAA/S score of 1 point were 56.08 (12.49) and 68.29 (12.65), respectively.
Conclusions: PLE shows potential as a hypnotic depth indicator during dexmedetomidine sedation, and its performance was not inferior to that of BIS.

1. Introduction

Objective and reliable monitoring techniques for assessing sedation depth are becoming increasingly important to prevent intraoperative awareness and postoperative delirium or cognitive impairment caused by inappropriate depth of sedation. Since the identification of the bispectral index (BIS; Bispectral Index™; Covidien, Boulder, CO, USA) in 1997, more than 10 such parameters have been used to date. Most of these parameters are derived from an algorithm based on analysis of the power of distinct electroencephalogram (EEG) frequency components [1,2]. However, a new measure, phase lag entropy (PLE; PLEM100™; InBody Co., Ltd., Seoul, Korea), which is a 4-channel EEG monitor, is based on a different unique algorithm. Recent studies have suggested that the complexity and diversity of directional communications between brain regions reflects the level of consciousness better than the strength of static connectivity. As sedation deepens, communicational diversity decreases, which is indicated by an increase in phase synchronization [3,4]. PLE calculates the diversity of the temporal patterns

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of the phase relationship by using EEG data from the frontal and prefrontal lobes, and it presents the level of consciousness as a number between 0 and 100 [3–5]. The performance of PLE as a hypnotic depth monitor under propofol sedation has been proven through several studies [5–9]. However, since different sedatives have different effects on EEG, the performance and reference values (cutoff points) must be evaluated separately for each sedative (ketamine, inhaled anesthetics, midazolam, etc.) [1,10,11]. Many studies have evaluated the performance of BIS with dexmedetomidine sedation in various clinical situations [12–17]. We have also confirmed the usefulness of BIS under dexmedetomidine sedation in previous studies [18]. This paper is an extension of our previous study [18], and we have reanalyzed the data collected during previous study to achieve the following objectives: (1) To evaluate the performance of PLE as a monitor of depth of sedation, in comparison with BIS, during sedation with dexmedetomidine. We hypothesized that PLE is not inferior to BIS. (2) To find an appropriate cutoff point of PLE for each sedation depth that can be used in clinical situations.

2. Materials and methods

2.1. Ethics statements

This study was approved by the Institutional Review Board of our hospital (BP IRB 2019-01-0137) and registered in the Clinical Research Information Service (CRIS) of South Korea (trial registration number: KCT 0006091). We obtained informed consent from each patient, and clinical research was conducted by following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013.

2.2. Study design

Forty-two patients aged between 20 and 80 years (American Society of Anesthesiologists physical status, class I–III) who were scheduled for elective surgery, such as transurethral vapor section for prostate cancer, transurethral bladder surgery for bladder cancer, or knee surgery, under spinal anesthesia were enrolled in this study. Patients with a history of cerebral nervous system diseases (such as epilepsy), uncontrolled hypertension or heart disease, chronic kidney disease (stage 4 or higher), or neuropsychiatric disorders; those who had difficulty in communicating; and those taking neuropsychiatric drugs were excluded.

We monitored non-invasive blood pressure, heart rate, EKG, and pulse oximetry data of the patients. Spinal anesthesia was performed using 0.5% bupivacaine (Marcaine® Spinal Heavy: 5 mg/mL; Astrazeneca, Södertälje, Sweden) 8–11 mg depending on the type of surgery. The peak sensory block level was evaluated every 2 min until the block heights of the spinal anesthesia showed no further changes. Oxygen (2–3 L/min) was supplied by nasal prongs, and end-tidal CO_2 was monitored.

Prior to dexmedetomidine administration, we applied both PLE and BIS sensors on the patient's forehead as recommended by the manufacturer and checked the baseline values of these indices for 2 min. Patient data (vital signs and values of PLE and BIS) were automatically stored in a computer in real time by using the Vital Recorder program [19]. One investigator, who was blinded to the study, conducted the assessment of the depth of sedation using the MOAA/S scale; a score of five points on the MOAA/S scale indicated that the patient was fully awake. The drug injection method was determined based on the prescription of dexmedetomidine, similar to the approach used in clinical practice. After intravenous administration of the loading dose (1.0 μg/kg for those aged <65 years and 0.5–0.75 μg/kg for those aged ≥65 years) for over 10 min, maintenance dose (0.3–0.6 μg/kg/h) was continuously infused intravenously. If the MOAA/S score dropped below 2 points during the loading dose infusion period, the maintenance-dose infusion was started before the planned loading dose was fully administered. The maintenance dose was adjusted within a range of 0.3–0.6 μg/kg/h to maintain the MOAA/S score at 3–4. When bradycardia (heart rate < 40 beats/min) occurred, we injected atropine 0.5 mg or ephedrine 5 mg intravenously. We checked the MOAA/S score every 3–5 min during the loading dose infusion period, and every 5–10 min during the maintenance dose infusion period. The administration of dexmedetomidine was stopped approximately 10–20 min before the surgery was completed, and the MOAA/S score was evaluated every 2–3 min to confirm the recovery of patient from sedation.

2.3. Data preparation

Data for analyses were prepared using the same method mentioned in the previous study [18]. The MOAA/S score was manually recorded every 3–6 min, and the values of PLE and BIS score were automatically recorded in a computer every second. Consequently, the three datasets were merged based on time to create data pairs (MOAA/S score-PLE value-BIS value data pairs) that were used for the analysis. Fig. 1 shows the process of organizing the actual data collected in this study. If the interval for evaluation of MOAA/S score was longer than 5 min, the PLE and BIS values obtained 2.5 min before and after checking the MOAA/S the score were included in the analysis. Furthermore, the PLE and BIS values that were not stored properly or those with low signal quality index (SQI) values were excluded from the analysis. Thus, the bias caused by the awakening of the patient due to the physical stimulus for assessing the MOAA/S score was reduced by including the PLE and BIS values before and after checking the MOAA/S scores.

2.4. Sample size calculation and statistical analysis

In a pilot study conducted with four patients and 1658 PLE and BIS data pairs, Bland–Altman analysis showed that the mean difference was 3.4 and the standard deviation (SD) of the difference was 6.8. We calculated the sample size based on this result by using a Bland–Altman plot (alpha, 0.05; 1 - power 0.2; maximum allowed difference between methods [mean + 1.96SD], 16.8) in MedCalc (version 17.1, MedCalc Software bvba, Mariakerke, Belgium), and the minimum required number of data pairs was 203,102.

We performed statistical analyses using MedCalc (version 18, MedCalc Software; Bvba, Ostend, Belgium) and GraphPad Prism (version 9, GraphPad Software; San Diego, USA). For baseline variability of PLE and BIS values, the relative standard deviation (RSD) was calculated using data obtained for 2 min before dexmedetomidine administration. The relationships between the MOAA/S scores and PLE or BIS values were examined using Spearman's correlation coefficients and prediction probability (P_k) values. The P_k was calculated with the Somers' d statistic using fit4NM 4.6.0. (Eun-Kyung Lee and Gyu-Jeong Noh; http://www.fit4nm.org/download/246; last accessed: 24 June 2014) as follows: P_k = (Somers' d + 1)/2. $P_k = 1$ indicated perfect agreement, and $P_k = 0.5$ indicated a random relationship. We calculated the average values of PLE and BIS for each MOAA/S score, and these values were compared using the *t*-test and one-way ANOVA. The correlation between PLE and BIS was assessed using Pearson's correlation coefficients and linear regression. We performed Bland–Altman analysis to examine the difference between the observed PLE and BIS values. Receiver operating characteristic (ROC) analysis was performed to measure the effectiveness (accuracy) of PLE and BIS as hypnotic indicators and to obtain optimal threshold values (cutoff points) of PLE and BIS to estimate depth of sedation (MOAA/S score) [20]. Quantitative data were expressed as mean (SD), or median and the 95th percentiles. *P* values <0.05 were considered statistically significant.

3. Results

A total of 42 participants consisting of 19 males and 23 females were enrolled in this study. The patients' mean (SD) age, height, and weight

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A.

Time	MOAA/S	PLE	BIS
11:39:27	4	92	85
11:39:28		91	85
11:39:29		91	85
11:42:00		82	76
11:42:01	4	82	77
11:42:02		82	77
11:42:03		82	77
11:42:04		80	77
11:44:48		74	73
11:44:49	3	74	74
11:44:50		74	74
11:44:51		74	75

B.

Time	MOAA/S	PLE	BIS
11:39:27	4	92	85
11:39:28	4	91	85
11:39:29	4	91	85
11:42:00	4	82	76
11:42:01	4	82	77
11:42:02	4	82	77
11:42:03	4	82	77
11:42:04	4	80	77
11:44:48	4	74	73
11:44:49	3	74	74
11:44:50	3	74	74
11:44:51	3	74	75

Fig. 1. The data preparation process for analysis. (A) Original MOAA/S data, which were manually recorded, and original PLE and BIS data, which were automatically recorded by a computer, were merged based on the time recorded. (B) Example of data pairs used in the analysis. MOAA/S: Modified Observer's Assessment of Alert/Sedation scale, PLE: phase lag entropy, BIS: bispectral index.

were 62.2 (11.8) years, 162.4 (8.0) kg, and 66.2 (11.7) cm, and the average time for the operation was 81.9 (39.1) min.

Both blood pressure and heart rate tended to decrease as the dexmedetomidine was intravenously administered (Fig. 2). In 22 patients, the heart rate decreased to <50 beats/min, and three of these patients had a heart rate <45 beats/min. Although heart rate decreased, blood pressure remained stable in most patients. However, in three patients, blood pressure was not stable (systolic blood pressure < 90 mmHg or mean blood pressure < 60 mmHg) and required drug treatment (injection of ephedrine intravenously). During sedation, the oxygen saturation of the patients was well maintained without any respiratory depression.

A total of 215,082 points of MOAA/S score, PLE and BIS data pairs were analyzed (MOAA/S = 5: 57,219 data pairs; MOAA/S = 4: 65,489 data pairs; MOAA/S = 3: 44,966 data pairs; MOAA/S = 2: 30,934 data pairs; MOAA/S = 1: 6,357 data pairs; and MOAA/S = 0:10,117 data pairs).

The baseline variabilities of PLE and BIS were 4.53% and 7.02%, respectively. When the MOAA/S score decreased, values of PLE and BIS also decreased, and Table 1 shows the correlation between the MOAA/S scale score and PLE or BIS. Fig. 3 presents the average values of PLE and BIS for each MOAA/S score. For MOAA/S scores of five, three, and one point, the mean (SD) values of PLE were 87.40 (9.19), 68.35 (15.68),

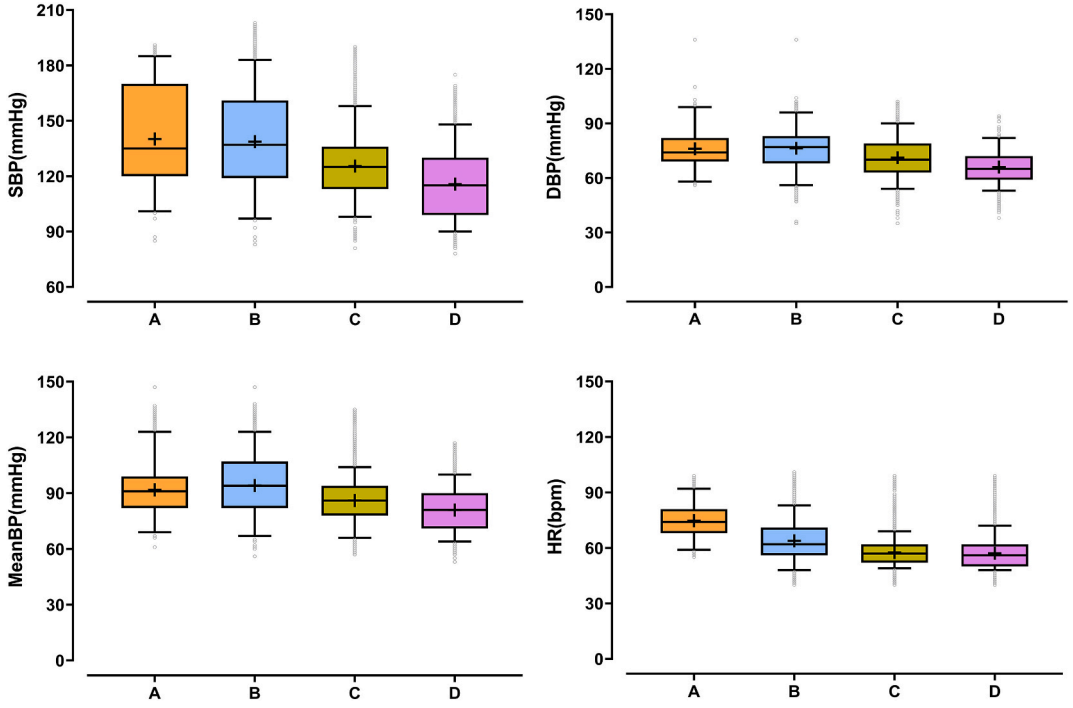

Fig. 2. Changes in blood pressure (BP) and heart rate (HR) during the study period, including the dexmedetomidine sedation period. (A) The period before dexmedetomidine administration (baseline). (B) During the loading dose infusion. (C) During the maintenance dose infusion. (D) The period after the end of dexmedetomidine infusion. In this box-and-whisker plot, the center line of the box represents the median value, the whiskers represent the 5th and 95th percentiles, the plus sign ('+') represents the mean value, and the gray dots indicate the individual values. SBP: systolic BP, DBP: diastolic BP. This figure contains the results presented in previous study [18].

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Table 1
The relationship between the modified observer's assessment of alert/sedation (MOAA/S) scores and phase lag entropy (PLE) or bispectral index (BIS) values.

	PLE	BIS
Spearman's coefficient of rank correlation	0.599	0.566
(95% CI)	(0.597–0.602)	(0.563–0.568)
Prediction probability	0.647	0.636
(95% CI)	(0.646–0.648)	(0.635–0.637)

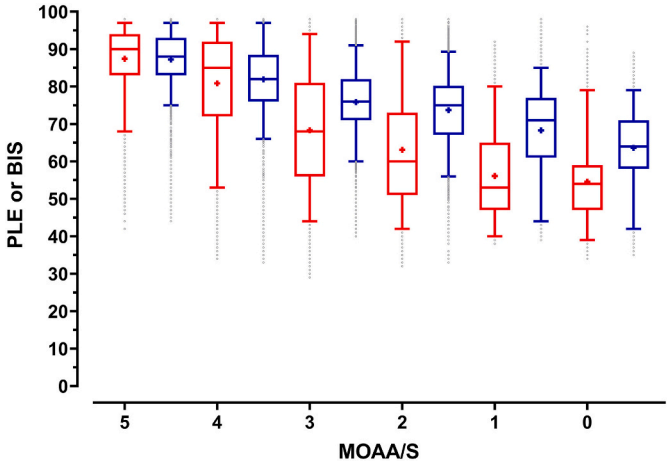

Fig. 3. The average values of PLE (phase lag entropy, red) and BIS (bispectral index, blue) for each MOAA/S (modified observer's assessment of alert/sedation) score. In this box-and-whisker plot, the center line of the box represents the median value, the whiskers represent the 5th and 95th percentiles, the plus sign ('+') represents the mean value, and the gray dots indicate the individual values. PLE: phase lag entropy BIS: bispectral index, MOAA/S: modified observer's assessment of alert/sedation scale. This figure contains the results presented in previous study [18]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and 56.08 (12.49), respectively ($P < 0.0001$, vs. PLE value at MOAA/S score 5 points, one-way ANOVA). The corresponding mean (SD) values of BIS were 87.22 (7.06), 75.85 (9.81), and 68.29 (12.65), respectively ($P < 0.0001$, vs. BIS value at MOAA/S score 5 points, one-way ANOVA). The PLE and BIS values at each sedation level (MOAA/S score) also showed statistically significant differences ($P < 0.0001$, paired *t*-test).

Fig. 4 shows the average PLE and BIS values at three time points (before and during the infusion of the drug and after stopping the drug infusion) when the MOAA/S score was 5 points. The findings confirmed that while the MOAA/S score remained the same (5 points), the average values of both PLE and BIS were different depending on whether the drug was administrated.

The Pearson's correlation coefficient between PLE and BIS was 0.706 (95% CI 0.704–0.708, P < 0.0001). Fig. 5 shows the results of the regression analysis to determine the correlation between PLE and BIS and the results of Bland–Altman analysis for evaluating the agreement between PLE and BIS.

Fig. 6 presents the area under the ROC curve (AUC) for the relationship between the PLE or BIS values and the MOAA/S score (≤3, ≤1, ≥3, and ≥ 1 point). Tables 2 and 3 present the data for the Youden Index and the results of the ROC analysis, and the cutoff points (criterion values of Youden Index) of PLE and BIS for specific sedation levels (MOAA/S score ≤ 3, ≤1, ≥3 and ≥ 1 point) have been determined.

4. Discussion

We found that PLE has potential as an indicator of hypnotic depth under dexmedetomidine sedation, and its performance is not inferior to that of BIS. The results of the ROC analysis demonstrated the accuracy of PLE and BIS for measurement of the depth of sedation (MOAA/S score). The AUC values for both PLE and BIS at specific sedation levels were over 0.7. For MOAA/S scores ≤3 and ≥ 3, the AUC values of PLE were higher than those of BIS (pairwise comparison of ROC curves, $P < 0.0001$). On the other hand, the AUC value of BIS was higher than that of PLE for MOAA/S scores ≥1 point (pairwise comparison of ROC curves, $P < 0.0001$).

Good correlation does not necessarily imply good agreement. As stated by Bland and Altman, the correlation coefficient *r* measures the strength of a relationship between two variables, not the agreement between them. In this study, although the correlation between PLE and BIS was good (Pearson's correlation coefficient = 0.706, linear regression $r = 0.71$), the mean difference between PLE and BIS derived from Bland–Altman analysis was significantly different from 0. Moreover, the mean values of PLE and BIS differed for each sedation level (MOAA/S score). When the MOAA/S score was 3 points, the PLE and BIS values were 68.35 and 75.85, respectively. However, when the MOAA/S score was 1 point, the PLE and BIS values were 56.08 and 68.29, respectively. The tendency of PLE values to appear lower than BIS values at the same level of sedation (MOAA/S score) was consistent with that reported in a

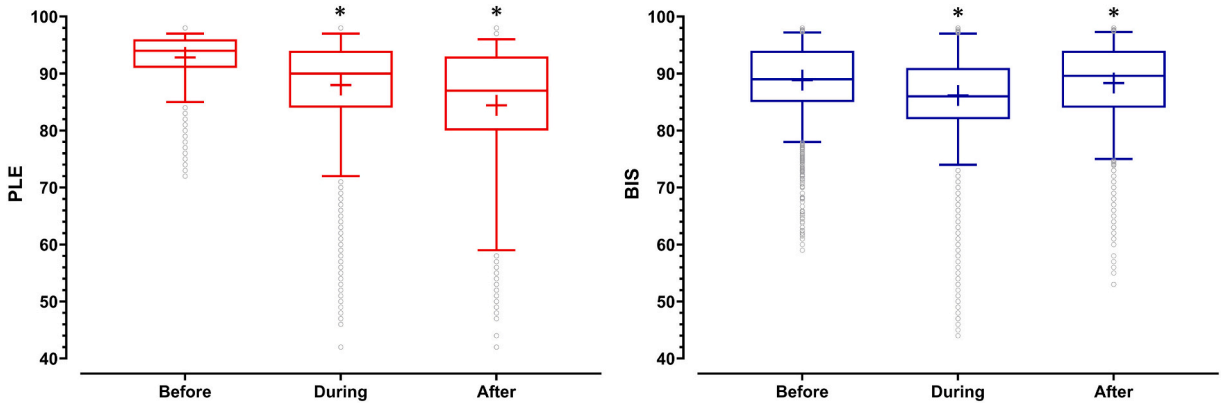

Fig. 4. The average values of PLE (phase lag entropy, red) and BIS (bispectral index, blue) when the MOAA/S (modified observer's assessment of alert/sedation) score is 5 points, divided according to the dexmedetomidine administration situation. The graph on the left shows the PLE values, and the graph on the right shows the BIS values. In this box-and-whisker plot, the center line of the box represents the median value, the whiskers represent the 5th and 95th percentiles, the plus sign ('+') represents the mean value, and the gray dots indicate the individual values. Before: before dexmedetomidine administration, During: while administering dexmedetomidine, including the loading and maintenance doses, After: after stopping the dexmedetomidine administration, PLE: phase lag entropy, BIS: bispectral index. *: $p < 0.05$, vs. Before, one-way ANOVA, Dunnett's multiple comparisons test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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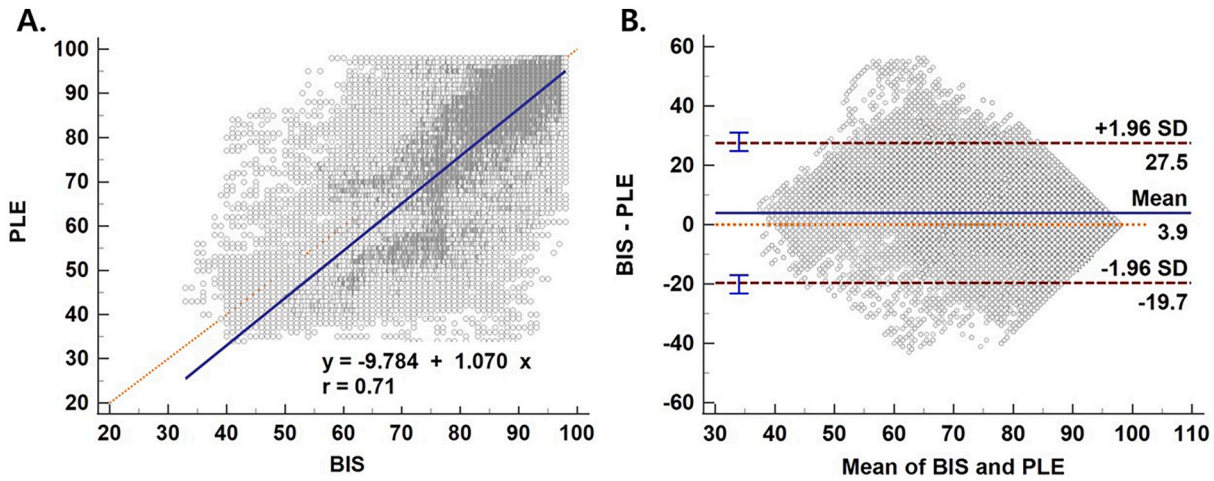

Fig. 5. The results of regression analysis and agreement analysis for PLE and BIS. (A) The linear regression line (blue solid line, y = 1.070× - 9.784, $r = 0.71$) for the correlation between PLE and BIS. The orange dotted line indicates "y = x," and the gray dots are the individual values.
(B) Bland-Altman plot for mean of BIS and PLE vs. (BIS−PLE), reflecting the agreement between PLE and BIS values. It contains 215,082 points of PLE and BIS paired data recorded from 42 participants (the gray dots). The orange dotted line indicates the similarity of the two indices, the blue solid line indicates the average difference between PLE and BIS, and the red dotted lines show the 95% limits of agreement. PLE: phase lag entropy, BIS: bispectral index. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

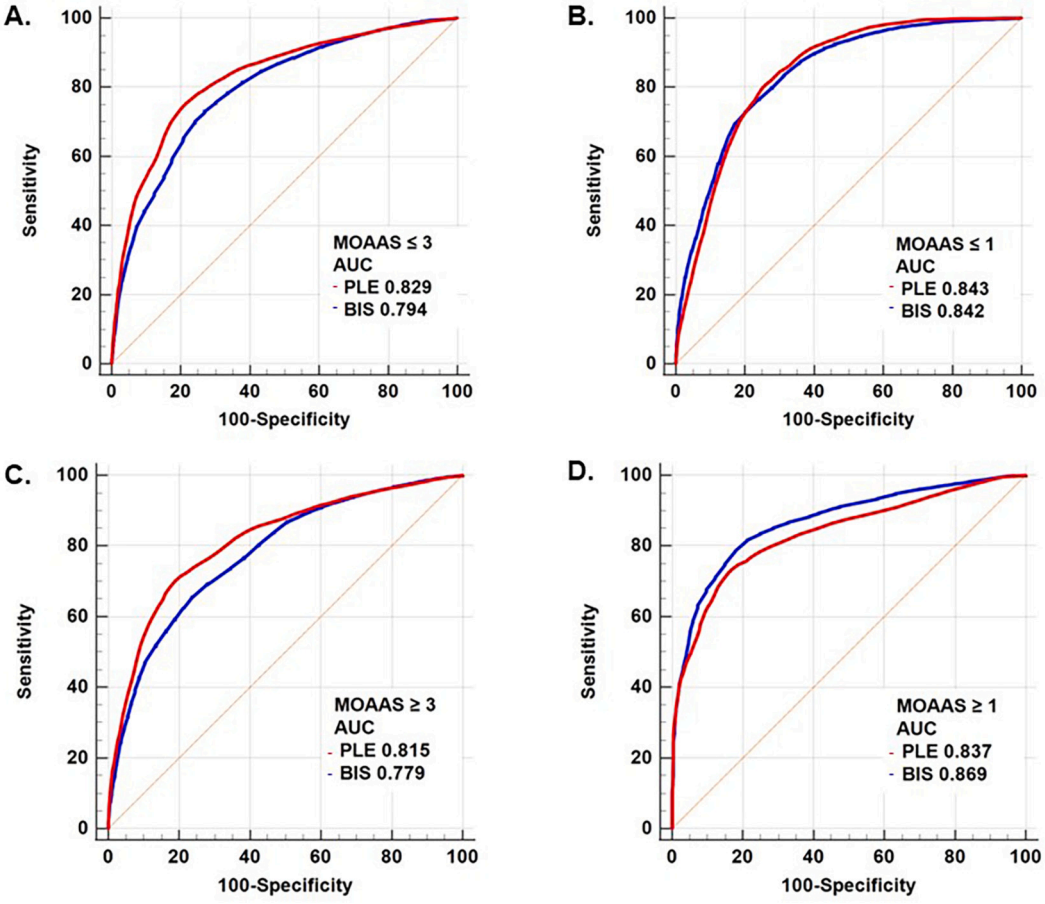

Fig. 6. Receiver operating characteristic (ROC) analysis showing the relationship between MOAA/S (modified observer's assessment of alert/sedation) scores and PLE (phase lag entropy, red) or BIS (bispectral index, blue). (A) ROC curve when the MOAA/S score is ≤3 points. (B) ROC curve when the MOAA/S score is ≤1 point. (C) ROC curve when the MOAA/S score is ≥3 points. (D) ROC curve when MOAA/S score is ≥1 point. PLE: phase-lag entropy, BIS: bispectral index, MOAAS: modified observer's assessment of alert/sedation scale, AUC: the area under the ROC curve. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Table 2
The results of receiver operating characteristic (ROC) analysis obtained from the association between the modified observer's assessment of alert/sedation (MOAA/S) scores of ≤3 and ≤ 1 points and the values of phase lag entropy (PLE) or bispectral index (BIS).

Classification variable		MOAA/S ≤ 3		MOAA/S ≤ 1	
		PLE	BIS	PLE	BIS
AUC		0.829	0.794	0.843	0.842
(95% CI)		(0.827–0.831)	(0.793–0.796)	(0.841–0.845)	(0.840–0.843)
Youden index	J	0.538	0.461	0.547	0.527
	(95% CI)	(0.535–0.542)	(0.457–0.464)	(0.541–0.553)	(0.520–0.533)
	Criterion value	≤ 75	≤ 79.9	≤ 64	≤ 73.5
	Sensitivity	75.21	73.09	79.66	72.94
	Specificity	78.59	72.97	75.03	79.72

AUC: the area under the ROC curve, J: the Youden Index J = max {sensitivity(c) + specificity(c) - 1}.

Table 3
The results of receiver operating characteristic (ROC) analysis obtained from the association between the modified observer's assessment of alert/sedation (MOAA/S) scores of ≥3 and ≥ 1 points and the values of phase lag entropy (PLE) or bispectral index (BIS).

Classification variable		MOAA/S ≥ 3		MOAA/S ≥ 1	
		PLE	BIS	PLE	BIS
AUC		0.815	0.779	0.837	0.869
(95% CI)		(0.813–0.816)	(0.777–0.780)	(0.835–0.839)	(0.868–0.871)
Youden index	J	0.511	0.418	0.564	0.608
	(95% CI)	(0.507–0.515)	(0.413–0.422)	(0.556–0.571)	(0.600–0.615)
	Criterion value	> 73	> 78.1	> 65	> 73
	Sensitivity	69.95	65.53	72.27	78.63
	Specificity	81.17	76.23	84.13	82.12

AUC: area under the ROC curve, J: Youden Index J = max {sensitivity(c) + specificity(c) - 1}.

previous study [5]. These results are thought to be due to differences in the algorithms for evaluation of these parameters from EEG data.

The algorithm by which PLE is obtained to evaluate the consciousness level is unique and different from those used for other parameters [3–7]. PLE calculates the diversity of the temporal patterns of the phase relationship of electro-encephalographic signals obtained from two channels at the prefrontal (FP1, FP2) and frontal (AF3, AF4) regions of the brain. The dynamics of the phase relationship between the prefrontal and frontal region channels become progressively less diverse and more stereotyped during unconsciousness, manifesting as a reduction in PLE [3]. The PLE (PLE100™) displays an index value between 0 and 100 in a linear scale for monitoring sedation depth. The algorithm for calculating the PLE index value consists of three weighted parameters, the PLE1 of αβ power (8–32 Hz), the PLE2 of γ power (32–45 Hz), and the burst suppression ratio (2–32 Hz). In the awake state, the distribution of phase patterns becomes difficult to predict and becomes irregular, thus yielding high PLE values. On the other hand, in the sedated state, the distribution of phase patterns is relatively even and regular, and the PLE value is decreased.

On the basis of a previous study in which dexmedetomidine and propofol showed different effects on EEG [10], we questioned whether the cutoff point of PLE and BIS for dexmedetomidine and propofol sedation were also different. Moreover, we aimed to determine the cutoff points for both PLE and BIS because the agreement between the two parameters was poor. We tried to find a cutoff point using Youden Index J statistics [20], and the results demonstrated that the cutoff points of PLE and BIS were different at specific sedation levels. Similar to the lower mean values of PLE than those of BIS at the same MOAA/S scores, the cutoff points of PLE for specific sedation level were also lower than those of BIS. At moderate sedation (MOAA/S score ≤ 3), the cutoff points of PLE and BIS were ≤75 and 79.9, respectively. At deep sedation (MOAA/S score ≤ 1), the cutoff points of PLE and BIS were ≤64 and 73.5, respectively. In the study by Ki [5], which evaluated the performance of PLE during propofol sedation, for 50% of the patients evaluated in the logistic regression model, the values of PLE and BIS at moderate sedation were 75.0 and 78.6, respectively, and the values of PLE and BIS at deep sedation were 59.5 and 67.0, respectively.

This study had some limitations. (1) Data on deep sedation (MOAA/S score ≤ 1) were relatively insufficient because the study was conducted in real operation situation. (2) The changes in raw EEG data were not observed. (3) The age of the participants did not vary.

Despite these limitations, our results indicate that the usage of PLE or BIS, which are parameters based on EEG changes, with clinical signs can help maintain an appropriate depth of sedation. Most importantly, however, the reliability of these monitoring approaches should be assessed in relation to the use of various sedatives and various clinical parameters (age, comorbidities, type of surgery etc.). In this study, our findings suggested that PLE can be useful for measurement of hypnotic depth in sedation using dexmedetomidine.

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Disclosure

The authors declare that they have no known competing financialinterestsor personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Sehun Lim: Conceptualization, Writing – original draft. **Kwangrae Cho:** Methodology, Formal analysis. **Wonjin Lee:** Methodology, Formal analysis. **Jinhyeok Kim:** Investigation, Writing – original draft. **Jongwook Bang:** Data curation. **Seunghee Ki:** Conceptualization, Formal analysis, Writing – review & editing, Supervision.

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