Research Article

A Crossover Comparison of the Sensitivity and the Specificity between BIS and AEP in Predicting Unconsciousness in General Anesthesia

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Background. There is an increasing concern of awareness and recall during general anesthesia for both the patient and the anesthetist. The bispectral index (BIS) is used to assess the level of sedation and depth of anesthesia and detect consciousness in different anesthetic drugs. Middle-latency auditory evoked potentials (AEPs) also quantify action of anesthetic drugs and detect the transition from consciousness to unconsciousness. We aim to compare the sensitivity and specificity between BIS and AEP in predicting unconsciousness in inhalational sevoflurane anesthesia and intravenous propofol anesthesia. *Methods*. Totally, 40 patients were randomly allocated into two groups: propofol or sevoflurane group. In the propofol group, anesthesia was induced with target-controlled infusion propofol. In the sevoflurane group, anesthesia was induced by increasing concentrations of sevoflurane. There were 3 end points during induction: sedation, unconsciousness, and anesthesia. Target and effect-site concentrations of propofol, end-tidal concentration of sevoflurane, and BIS and AEP were recorded at each stage. *Results*. We obtained good EC50 with both monitors, at which there is a 50% chance that the patient has reached the end point, but the index variation was affected by the anesthetic technique. Propofol had higher correlations with stage of anesthesia, BIS, and AEP than sevoflurane. BIS had higher correlations with depth of anesthesia than AEP, but we did not find an anesthetic depth monitor that had high sensitivity and specificity and is not affected by the anesthetic technique. *Conclusions*. The prediction powers of BIS and AEP do not seem as good as some papers mentioned.

1. Introduction

Awareness and recall during general anesthesia, which are unintended accidental, represent failure of successful anesthesia and cause a serious complication of general anesthesia that is feared by patients and anesthetists alike [1–3]. It is difficult to describe and identify return to consciousness, so the reported incidence rates vary widely. Evidence suggests that the overall risk of awareness during anesthesia is between 0.1 and 0.5% [2, 4–6], and awareness has been considered as a potentially important factor for the occurrence of some diseases in patients, such as severe emotional distress and posttraumatic stress disorder [4, 6–8]. It also has important professional, personal, and financial consequences for the anesthetists [8–11].

The bispectral index (BIS), derived from electroencephalogram, is the most commonly used and accepted monitor for assessing the level of sedation and depth of anesthesia [10, 12–15]. BIS predicts movement in response to surgery and detects consciousness under different anesthetic drugs [15–18]. It is also a tool that may reduce the incidence of unexpected recall [10, 12, 13, 18].

Middle-latency auditory evoked potentials (AEPs) also quantify the action of anesthetic drugs and detect the transition from consciousness to unconsciousness [19–23]. The AEP index (AEP) is a dimensionless number scaled from 100 (awake) to 0 and a mathematically derived variable measuring the amplitude and latency of the cortical mid-latency auditory evoked potential that occurs in response to sound (a "click") [21, 23, 24].

Sevoflurane inhalational and propofol intravenous anesthesia are two widely used anesthetic techniques. However, there are no reports about the comparison of ability of predicting the awareness by BIS or AEP during these two anesthesia techniques. Herein, this study is designed to compare the sensitivity and the specificity between BIS and AEP in predicting unconsciousness with sevoflurane inhalational and propofol intravenous anesthesia.

2. Materials and Methods

The study was approved by the institutional review board. Unpremedicated patients who had given informed consent were recruited into the study. Demographic data and ASA classification were recorded. Routine monitoring plus monitoring for BIS and AEPi was established before the induction of anesthesia. Awake values for BIS and AEPi were recorded before the induction of anesthesia. Patients breathed oxygen through a standard anesthetic breathing circuit during induction. Patients were randomised into propofol or sevoflurane groups. There were 3 end points during induction:

(1) Sedation: patent was asleep and responded to gentle shaking or loud auditory stimulus (stage 4 of Ramsay scale).

(2) Loss of consciousness: patient showed no response to verbal command and loss of eyelash reflex.

(3) Anesthesia: patient gave no purposeful movement on tetanic stimulation to the ulnar nerve (50 Hz, 80 mA, 0.25 ms pulses) at the wrist using a constant current peripheral nerve stimulator.

The BIS and AEPi were recorded at each stage. In the propofol group, anesthesia was induced with target-controlled infusion (TCI) propofol. The TCI was initially set at $1 \mu g \cdot l^{-1}$ and increased by $0.5 \mu g \cdot l^{-1}$ every 2 minutes until anesthesia. Target and effect-site concentrations of propofol were recorded at each end point. In the sevoflurane group, anesthesia was induced by increasing concentrations of sevoflurane. End-tidal concentration of sevoflurane was recorded at each end point.

2.1. Anesthesia Induction. Routine monitoring plus monitoring for BIS and AEP was established before the induction of anesthesia. Awake values for BIS and AEP were recorded before the induction of anesthesia. Patients breathed oxygen through a standard anesthetic breathing circuit during induction. Patients were randomised into propofol or sevoflurane groups. There were 3 end points during induction: (1) sedation: patient was asleep and responded to gentle shaking or loud auditory stimulus (stage 4 of Ramsay scale); (2) unconsciousness: patient showed no response to verbal command and loss of eyelash reflex; (3) anesthesia: patient gave no purposeful movement on tetanic stimulation to the ulnar nerve (50 Hz, 80 mA, 0.25 ms pulses) at the wrist using a constant current peripheral nerve stimulator. The BIS and AEP were recorded at each stage. In the propofol group, anesthesia was induced with target-controlled infusion (TCI) of propofol. The TCI was initially set at $1 \mu g \cdot l^{-1}$ and

increased by $0.5 \mu g \cdot l^{-1}$ every 2 minutes until anesthesia. Target and effect-site concentrations of propofol were recorded at each end point. In the sevoflurane group, anesthesia was induced by increasing concentrations of sevoflurane. End-tidal concentration of sevoflurane was recorded at each end point.

2.2. Statistical Analysis. GraphPad Prism version 5 (GraphPad Software, Inc) was used for data analysis. Demographic data were analyzed by the chi-square test and *t*-test. Haemodynamic data were analyzed by repeated measures analysis of variance and post hoc pair-wise comparison for difference stages of anesthesia. Spearman correlation analysis, logistic regression analysis, receiver operating characteristic (ROC) analysis, sensitivity and specificity, and prediction probability (P_K) were used for analyzing the depth of anesthesia, drug concentration, BIS, and AEP. $P < 0.05$ was considered to have statistically significant difference.

3. Results

3.1. Patient Characteristics. Forty-two patients were assessable for intraoperative BIS and AEP data, including 22 patients with sevoflurane anesthesia and 20 patients with propofol anesthesia. Two patients of the sevoflurane group were censored because of the unreasonable high BIS and AEP in the anesthesia stage. One patient of the sevoflurane group swapped the effect-site concentrations on sedation and unconsciousness because of the unreasonable high concentrations (4 and 4.6 mcg/ml) in the sedation stage. No significant difference in gender, height, weight, smoking history, alcohol intake, pain in sedation stage, or American society of Anesthesiologists status was found between two groups (Table 1).

3.2. Haemodynamic Data. Systolic blood pressure (SBP), heart rate (HR), and respiratory data (RR) in two groups were analyzed in four stages: base, sedation, unconsciousness, and anesthesia (Tables 2 and 3 and Figure 1). For SBP, time effect was significantly different at the 0.05 level of significance. Time and group interaction effect was significantly different at the 0.01 level of significance. On the propofol group, the SBP on all the other stages was significantly different from the baseline ($P = 0.0003$, <0.0001, and <0.0001 in sedation, unconsciousness, and anesthesia stages, respectively). The SBP on the sedation stage was also significantly different from the SBP on the unconsciousness and anesthesia stages. On the sevoflurane group, the SBP on all the other stages was significantly different from the baseline ($P = 0.0354$, 0.0053, and 0.0031 in sedation, unconsciousness, and anesthesia stages, respectively). The SBP on the sedation stage was significantly different from the SBP on unconsciousness and anesthesia stages.

On HR, both time effect and group interaction effects were significantly different at the 0.05 level of significance. On the propofol group, the heart rates on all the other stages were significantly different from the baseline heart rate

TABLE 1: Patient characteristics.

	Mean (SD) [range]/counts		
	Propofol group	Sevoflurane group	P value
Patient no.	20	20	N.A.
Age (years old)	27 (8.6) [17–46]	28 (11.3) [18–49]	0.7422
Weight (Kg)	60 (13.7) [41–85]	56 (7.1) [46–69]	0.3466
Sex ratio (male : female)	10 : 10	12 : 8	0.5250
ASA grading (I : II)	18 : 2	18 : 2	1.0000
Smoker	2	2	1.0000
Alcohol (no: occasional)	19 : 1	19 : 1	1.0000
Pain in sedation stage (none: mild: moderate)	11 : 8 : 1	No data	N.A.

ASA, American society of Anesthesiologists; N.A., not applicable.

TABLE 2: Haemodynamic data.

	Stage	Mean ± SD		P values
		Propofol	Sevoflurane	
Systolic blood pressure (SBP) in HHmg	Base	117.6 ± 12.7	117.1 ± 15.3	Group: 0.4542 Time: <0.0001** Interact: 0.0542
	Sed	112.2 ± 11.8	112.5 ± 11.1	
	Uncon	105.8 ± 8.8	109.4 ± 10.4	
	Anes	102.0 ± 7.4	108.4 ± 11.2	
Heart rate (HR) in beat min^{-1}	Base	80.5 ± 10.7	79.6 ± 10.4	Group: 0.0784 Time: 0.0596 Interact: 0.0118**
	Sed	76.7 ± 8.6	81.0 ± 11.4	
	Uncon	72.2 ± 10.1	79.2 ± 13.1	
	Anes	72.9 ± 11.7	84.4 ± 14.9	
Respiratory rate (RR) in breaths min^{-1}	Base	18.3 ± 3.2	17.0 ± 3.1	Group: 0.0964 Time: 0.4993 Interact: 0.9212
	Sed	17.9 ± 2.6	16.6 ± 2.6	
	Uncon	18.2 ± 2.4	16.7 ± 2.7	
	Anes	18.2 ± 2.7	17.1 ± 2.7	

**Significant at 0.05. Notes: repeated measures analysis of variance was applied. Interact = group*time interaction effect.

TABLE 3: P values for post hoc pair-wise comparisons.

	P values		
	Baseline	Sedation	Unconsciousness
SBP			
Time effect in propofol group			
Sedation	0.0003**	—	—
Unconsciousness	<.0001**	<.0001**	—
Anesthesia	<.0001**	0.0001**	0.0167
Time effect in sevoflurane group			
Sedation	0.0354	—	—
Unconsciousness	0.0053**	0.0493	—
Anesthesia	0.0031**	0.0355	0.4102
HR			
Time effect in propofol group			
Sedation	0.0266	—	—
Unconsciousness	0.0034**	0.0133	—
Anesthesia	0.0188	0.0610	0.6775
Time effect in sevoflurane group			
Sedation	0.5275	—	—
Unconsciousness	0.8083	0.1995	—
Anesthesia	0.2306	0.1517	0.0122**

Adjusted $\alpha' = 0.0125$ (=0.05/4) for post hoc comparisons **$P < 0.01$.

($P = 0.0266$, 0.0034, and 0.0188 in sedation, unconsciousness, and anesthesia stages, respectively). The heart rate on the sedation stage was also significantly different from the heart rate on the unconsciousness stage ($P = 0.0133$). On the sevoflurane group, there were not significantly different in all different stages.

3.3. Drug Concentrations, BIS, and AEP

3.3.1. Descriptive Statistics of Drug Concentrations, BIS, and AEP at Different Stages of Induction. redicted blood and effect-site propofol concentrations and inspired and end-tidal sevoflurane concentrations during different stages of induction are shown in Table 4. Both BIS and AEP showed a trend of diminishing level of consciousness with both anesthetic techniques.

3.3.2. Correlation Analysis. On correlation analysis of BIS and AEP vs. propofol and sevoflurane concentration, only 6 correlation coefficients in the propofol group were significant at the 0.05 level of significance. $r = -0.50$, -0.49, and -0.45 when BIS is in the unconsciousness stage vs. predicted blood concentration of propofol in sedation, anesthesia stages, and effect-site concentration of propofol in the anesthesia stage, respectively. $r = 0.56$ when AEP is in the anesthesia stage vs. predicted blood concentration and effect-site concentration of propofol in the unconsciousness stages, and $r = -0.53$ when AEP of baseline vs. effect-site concentration of propofol is in the sedation stage. They were around 0.5, just fair correlated. All the others are not significantly correlated (Tables 5 and 6). On correlation analysis
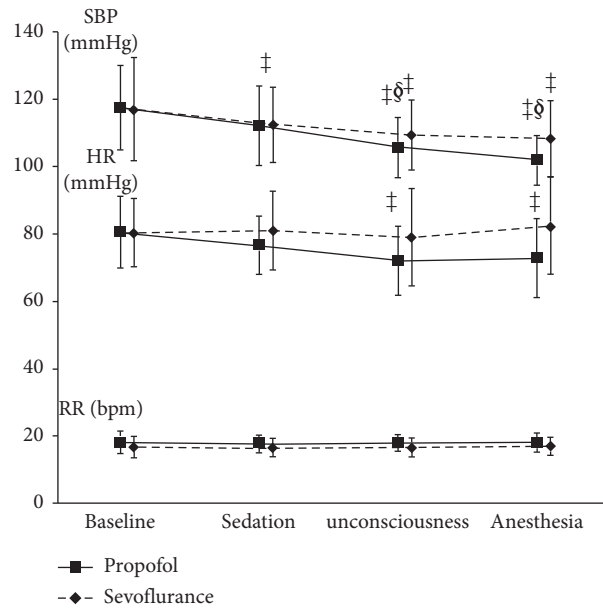
FIGURE 1: Systolic blood pressure (SBP), heart rate (HR), and respiratory data (RR) of two groups in four stages: base, sedation, unconsciousness, and anesthesia. On SBP, time effect was significantly different at the 0.05 level of significance; time and group interaction effect was significantly different at the 0.01 level of significance. On HR, both time effect and group interaction effects were significantly different at the 0.05 level of significance. On RR, no difference was found in both time effect and interaction effect. ‡ indicates significant difference from baseline. § indicates significant difference from sedation. † indicates significant difference from unconsciousness. On RR, no difference was found in both time effect and interaction effect.

of BIS vs. AEP, only two correlation coefficients in the sevoflurane group were significant at the 0.05 level of significance. $R = 0.66$ when BIS in baseline vs. AEP in the baseline stage, and $r = 0.52$ when BIS in the unconsciousness stage vs. AEP in the anesthesia stage. All the others are not significantly correlated (Tables 7 and 8).

Both monitors showed a trend of diminishing level of consciousness with both anesthetic techniques. The index showed good correlation with stage of induction (Table 9), except with AEP when used with sevoflurane which gave a low correlation coefficient of -0.61 and a 95% CI crossing -0.5. Results showed that propofol had higher correlations between stage of anesthesia and BIS and AEP than sevoflurane. BIS had higher correlations with depth of anesthesia than AEP (given the prior probabilities for the sedation/unconsciousness/anesthesia to be 0.5).

Effective concentrations EC5, EC50, and EC95 referred to drug concentration at which 5%, 50%, and 95% of the patients, respectively, reached the predefined end point. EC5, EC50, and EC95 of predicted blood and effect-site propofol and inspired and end-tidal sevoflurane as well as BIS and AEP values at sedation, unconsciousness, and anesthesia and their sensitivity, specificity, and P_K values are shown in Tables 10–12, respectively. Effect-site propofol concentration had a smaller 95% CI of EC50 than that of blood at all stages from sedation to anesthesia. This difference is not noticed between inspired and end-tidal sevoflurane. BIS gave similar 95% CI of EC50 with propofol and sevoflurane at sedation and unconsciousness, but a range of smaller values with sevoflurane at anesthesia. For AEP, propofol always showed a range of smaller values from sedation to anesthesia.

P_K is the probability that the indicator values of the data points predict correctly which of the data points are the lighter (or deeper). A value of $P_K = 0.5$ means that the indicator correctly predicts the anesthetic depths only 50% of the time, i.e., no better than a 50:50 chance. A value of $P_K = 1$ means that the indicator predicts the anesthetic depths correctly 100% of the time.

3.3.3. Predicting Power. Table 13 shows the P_K for depth of anesthesia measured by the two monitors, BIS and AEP with different anesthetic techniques, propofol and sevoflurane. BIS had good P_K values with both propofol and sevoflurane with both above 0.8, and the P_K with propofol was better than that with sevoflurane. On the contrary, AEP did not have good P_K values, especially with sevoflurane. The P_K values with BIS are significantly better than those with sevoflurane. The prediction powers of BIS and AEP do not seem as good as some papers mentioned ($P_K > 0.9$).

4. Discussion

In this study, we investigated the usefulness and consistency of two anesthetic depth monitors, BIS and AEP with different anesthetic techniques, propofol intravenous anesthesia and sevoflurane inhalational anesthesia. BIS and AEP are two popular anesthetic depth monitors. It is important for them to perform consistently with different anesthetic techniques.

EC50 is analogous to the concept of minimum alveolar concentration for volatile anesthetics and is defined as the concentration of an i.v. anesthetic agent at which 50% of the

Table 4: Descriptive statistics of drug concentrations, BIS, and AEP at different stages of induction.

Mean ± SD, median (range)	Predicted blood concentration μg·ml⁻¹		Effect-site concentration μg·ml⁻¹		BIS		AEP	
Stage	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
Baseline	—	—	—	—	96.5 ± 3.19 97.5 [84–98]	96.6 ± 2.01 97 [90–98]	83.0 ± 10.6 82 [58–99]	79.4 ± 12.64 78.5 [48–99]
Sedation	2.0 ± 0.44 2 [1.5–3.0]	2.7 ± 0.72 2.6 [1.2–3.8]	1.2 ± 0.29 1.2 [0.7–1.7]	1.6 ± 0.53 1.55 [0.6–2.45]	81.2 ± 6.36 82 [64–93]	83.8 ± 14.63 86.5 [41–98]	58.1 ± 23.10 60 [20–95]	63.1 ± 19.45 65.5 [25–99]
Unconsciousness	3.5 ± 0.83 3.5 [2.0–5.5]	3.4 ± 0.62 3.4 [2.4–4.6]	2.4 ± 0.62 2.4 [1.2–3.7]	2.3 ± 0.68 2.25 [1.3–3.95]	58.0 ± 10.33 56.5 [40–74]	59.2 ± 19.18 60 [19–86]	34.1 ± 14.45 30 [10–55]	51.7 ± 20.02 46 [22–89]
Anesthesia	4.2 ± 0.98 4 [2.5–6.0]	4.1 ± 0.87 3.95 [2.6–5.95]	3.2 ± 0.81 3.25 [1.7–4.9]	3.0 ± 0.79 3.1 [1.7–4.25]	47.8 ± 8.67 46.5 [36–66]	41.05 ± 16.05 40 [14–72]	17.78 ± 5.97 17.5 [8–29]	38.7 ± 22.97 30.5 [12–83]

Table 5: BIS and AEP vs. propofol.

Propofol		Correlation coefficient, r							
		BIS				AEPi			
		Base	Sedation	Unconc	Anes	Base	Sedation	Unconc	Anes
Pred	Sedat	0.21	−0.06	−0.50**	−0.02	−0.22	0.08	0.24	0.34
	Unconc	0.40	0.27	−0.34	−0.12	−0.17	0.19	0.29	0.56**
	Anesthesia	0.44	0.30	−0.49**	−0.35	−0.14	0.15	0.33	0.43
Eff	Sedat	0.22	0.09	−0.30	−0.31	−0.53**	0.08	0.10	0.35
	Unconc	0.42	0.27	−0.26	−0.16	−0.23	0.09	0.22	0.56**
	Anesthesia	0.43	0.33	−0.45**	−0.35	−0.25	0.05	0.20	0.39

**Significantly different from $r = 0$ at the 0.05 level. $r = 1$ or $−1$ means perfect correlation. $r = 0$ means no correlation.

Table 6: BIS and AEP vs. sevoflurane.

Sevoflurane		Correlation coefficient, r							
		BIS				AEPi			
		Base	Sedation	Unconc	Anes	Base	Sedation	Unconc	Anes
Pred	Sedat	−0.11	−0.19	−0.14	−0.17	0.01	−0.02	0.24	0.26
	Unconc	0.04	0.15	−0.003	−0.07	−0.03	−0.10	0.05	0.04
	Anes	0.07	0.05	−0.10	−0.25	−0.12	−0.11	−0.01	−0.03
Eff	Sedat	−0.21	−0.25	−0.16	−0.33	−0.24	−0.23	0.10	0.08
	Unconc	−0.19	−0.03	−0.13	−0.09	−0.22	−0.22	−0.05	−0.10
	Anes	−0.05	0.04	−0.01	−0.18	−0.09	−0.01	0.09	−0.00

Table 7: Correlation analysis of BIS vs. AEPi in the propofol group.

Propofol		Correlation coefficient, r			
		BIS			
		Base	Sedation	Unconc	Anes
AEPi	Base	−0.10	0.04	−0.10	−0.001
	Sedation	0.22	0.40	0.32	−0.01
	Unconc	0.23	0.25	0.37	0.27
	Anesthesia	0.17	0.14	0.30	0.29

Table 8: Correlation analysis of BIS vs. AEPi in the sevoflurane group.

Sevoflurane		Correlation coefficient, r			
		BIS			
		Base	Sedation	Unconc	Anes
AEPi	Base	0.66**	0.27	0.18	0.14
	Sedation	0.29	0.23	0.17	0.18
	Unconc	0.33	0.26	0.38	0.17
	Anesthesia	0.16	0.12	0.52**	0.21

** Significant different from $r = 0$ at the 0.05 level. $r = 1$ or -1 means perfect correlation. $r = 0$ means no correlation.

Table 9: Correlation of depth of anesthesia (4 stages, including baseline) vs. BIS and AEP.

	Spearman correlation coefficient, r [95% CI]		P value (H_0: $s_{sevo} = s_{prop}$)
	Propofol	Sevoflurane	
BIS	−0.92** [−0.87, −0.95]	−0.86** [−0.79, −0.91]	<0.05**
AEP	−0.80** [−0.71, −0.87]	−0.61** [−0.45, −0.73]	<0.05**
P value (H_0: $s_{BIS} = s_{AEP}$)	<0.05**	<0.05**	

Standard errors (SE) for the above s are 0.11. ** Significantly different from $s = 0$ at 0.05.

patients will not move or respond to skin incision. This clinically useful concept allows prediction of propofol concentration in the blood and at the effect site [25, 26].

We defined the anesthesia stage as when the patient showed no gross purposeful movement to tetanic stimulation of the ulnar nerve, which was easy to perform and had the advantage over skin incision as a repeatable stimulus. A study showed no significant difference between the effective concentration of propofol which prevented half of the patients to move (EC_{50}) at tetanic stimulation and that at skin incision in somatic response, but significant differences in haemodynamic response [25, 26]. Tetanic stimulation was useful in this study as a reproducible and repeatable stimulus at different propofol and sevoflurane concentrations. Similar to the results from Milne's group, the range of effect-site concentrations to include 90% of patients (EC5–EC95) was smaller than the predicted blood concentration range and hence a more useful figure to guide propofol administration [27]. Similarly, in the sevoflurane group, the range of end-tidal concentrations was smaller than the inspired, but to a lesser extent. Both monitors had distinctly different EC50s with small 95% CI. BIS had similar EC50s with both propofol and sevoflurane, but AEP showed different values between the two anesthetic techniques.

In this study, 90% of the patients were sedated at a BIS value between 90 and 71 with propofol or between 100 and 60 with sevoflurane. This indicates that BIS is therefore better at predicting sedation with propofol. AEP showed very wide range of values in order to induce 90% of the patients at sedation with both propofol (AEP value range 100-11) and sevoflurane (AEP value range 96-27), and therefore, AEP did not seem to be useful in guiding sedation. At unconsciousness, BIS showed a smaller range with propofol (BIS value range 77-37) than with sevoflurane (BIS value range 93-23), which might again indicate that BIS performs better with propofol. AEP showed a wide range with both propofol (AEP value range 61-4) and sevoflurane (AEP value range 85-12) at unconsciousness. At anesthesia, BIS again had a smaller range with propofol (BIS value range 61-31) than with sevoflurane (BIS value range 67-11). AEP showed a narrow range with propofol (AEP value range 28-6) but a wide one with sevoflurane (AEP value range 75-0). BIS appeared to be a good indicator of depth of anesthesia with propofol, which was reflected by the high P_K value of 0.91. Anesthetic seemed to have an effect on performance of the monitors, particularly with AEP monitor. BIS overall performed well with both anesthetic techniques, i.v. propofol and inhalational sevoflurane, but with a higher P_K with propofol. AEP showed poorer performance than BIS in our study. With a P_K of 0.56 with sevoflurane, AEP became doubtful as an anesthetic depth monitor which means the prediction powers of BIS and AEP do not seem as good as some papers mentioned [21, 22, 28, 29]. Considering the difference results between this study and previous ones, different protocols of studies might be the reason [22, 28–30]. We use detected more drug concentrations at more time points with more accurate statistical methods, but we still think we need more studies to verify the results. And this result might remind the clinicians that both BIS and AEP are not as reliable as they thought.

In summary, we obtained good EC50 with both monitors, but the index variation was affected by the anesthetic technique. The performance of the anesthetic depth monitors was better when propofol was used. Very wide variation was found in the combination of AEP and sevoflurane [22, 25, 31–33]. It seems the monitors are at best at giving the EC50, at which there is a 50% chance that the patient has reached the end point, and we have not yet found an anesthetic depth monitor that has high sensitivity and specificity and not affected by the anesthetic technique.

TABLE 10: Propofol/sevoflurane concentration, BIS/AEP values, and prediction probabilities at sedation (mean (95% CI)).

	EC5		EC50		EC95		Sensitivity (%)		Specificity (%)		Prediction probability (P_K)	
	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
Blood concentration (g/ml)/Fi (%)	0.9	1.2	1.7 (1.5–1.9)	2.5 (2.4–2.7)	2.6	3.9	92	82	64	72	0.78	0.75
Effect-site concentration (g/ml)/ET (%)	0.6	0.6	1.1 (1.1–1.2)	1.6 (1.5–1.7)	1.6	2.5	73	76	77	75	0.77	0.76
BIS	90	100	81 (80–82)	85 (82–87)	71	60	80	63	77	84	0.78	0.73
AEP	100	96	56 (52–60)	62 (58–65)	11	27	76	82	75	69	0.76	0.76

Table 11: Propofol/sevoflurane concentration, BIS/AEP values, and prediction probabilities at unconsciousness (mean (95% CI)).

	EC5		EC50		EC95		Sensitivity (%)		Specificity (%)		Prediction probability (P_K)	
	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
Blood concentration (g/ml)/Fi (%)	1.9	2.3	3.2 (3–3.4)	3.3 (3.2–3.4)	4.5	4.3	85	79	81	66	0.83	0.72
Effect-site concentration (g/ml)/ET (%)	1.3	1.1	2.3 (2.2–2.4)	2.2 (2.1–2.3)	3.3	3.3	83	79	73	75	0.78	0.77
BIS	77	93	57 (55–59)	58 (54–61)	37	23	79	77	72	77	0.76	0.77
AEP	61	85	32 (30–35)	48 (45–52)	4	12	71	68	79	82	0.75	0.75

TABLE 12: Propofol/sevoflurane concentration, BIS/AEP values, and prediction probabilities at anesthesia (mean (95% CI)).

	EC5		EC50		EC95		Sensitivity (%)		Specificity (%)		Prediction probability (P_K)	
	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane	Propofol	Sevoflurane
Blood concentration (g/ml)/Fi (%)	2.3	2.4	4 (3.7–4.2)	3.9 (3.8–4.1)	5.6	5.4	89	79	73	73	0.81	0.76
Effect-site concentration (g/ml)/ET (%)	1.7	1.6	3.1 (3–3.1)	3 (2.8–3.1)	4.5	4.4	76	78	76	75	0.76	0.76
BIS	61	67	46 (45–48)	39 (37–42)	31	11	73	76	76	75	0.74	0.76
AEP	28	75	17 (16–18)	34 (30–37)	6	0	81	66	72	83	0.77	0.75

TABLE 13: Prediction probability P_K for the depth of anesthesia (considering 4 stages including baseline).

| | P_K (SE) [P values for testing $P_K = 0.5$] | | P value [H_0: $P_{KBIS} = P_{KAEP}$] |
	BIS	AEP	
Propofol	0.9117 (0.0147) [$P < 0.0001^{**}$]	0.7504 (0.0238) [$P < 0.0001^{**}$]	$<0.0001^{**}$
Sevoflurane	0.8233 (0.0182) [$P < 0.0001^{**}$]	0.5629 (0.0391) [$P < 0.0001^{**}$]	$<0.0001^{**}$

**Significantly different from $s = 0$ at 0.05.

Data Availability

All the underlying data supporting the results of this study can be found in IRB of Second Affiliated Hospital of Dalian Medical University.

Disclosure

Haitao Yang and Guan Wang are the co-first authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Haitao Yang and Guan Wang contributed equally to this work.

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