Original Article

Simultaneous Anesthetic Depth Monitoring Using Noxious Stimulation Response Index and Bispectral Index: A Preliminary Report of a Prospective Observational Study in Clinical Settings

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ABSTRACT

Introduction: Anesthetic depth monitors, such as the bispectral index (BIS) monitor, are based on the analyses of electroencephalogram. SmartPilot View, another type of anesthetic depth monitor, calculates the effect-site concentration of anesthetics based on pharmacokinetic/pharmacodynamic simulations, computes the pharmacodynamic interaction between hypnotics and opioids, and displays the noxious stimulation response index (NSRI). NSRI is, thus, completely different from BIS as an anesthetic depth index. This study aimed to elucidate the predictability of BIS from NSRI.

Methods: We recorded the BIS values when the NSRI values ranged from 0 to 20, 21 to 50, 50 to 70, 71 to 90, and 91 to 100 in patients under desflurane/opioid anesthesia (group D, n = 20) and those under propofol/opioid anesthesia (group P, n = 20). We examined the predictability of BIS from NSRI using linear regression analysis.

Results: In both groups, linear regression analysis demonstrated the difficulty in the prediction of BIS from NSRI. Many patients in both groups showed a BIS value of 60 or less when the NSRI values ranged from 71 to 100 and a BIS value of less than 40 when the NSRI values ranged from 0 to 20.

Conclusions: It is difficult to predict BIS from NSRI, and the observed discrepancies between NSRI and BIS suggest that simultaneous monitoring of NSRI and BIS might have clinical utility in guiding appropriate anesthetic depth.

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KEYWORDS: SmartPilot View, effect-site concentration, pharmacokinetic/pharmacodynamic simulation, bispectral index monitor, electroencephalogram

Introduction

Evaluation of anesthetic depth is currently one of the challenges in anesthesiology.[1] Anesthetic depth should be adequately maintained to prevent adverse events associated with surgery. There are three major objectives of an-

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esthetic depth monitoring. First is to prevent accidental awareness during general anesthesia (AAGA) due to inappropriately light anesthesia. AAGA causes long-lasting adverse psychological effects, such as nightmares, anxiety, depression, and post-traumatic stress disorder.[2] Second is to prevent adverse sequelae related to excessively deep anesthesia. Excessively deep anesthesia causes circulatory suppression, and hypotension is an independent risk factor of postoperative morbidity and mortality.[3, 6] In addition, recent studies have suggested the correlation between deep anesthesia and postoperative cognitive disorders.[7, 8] Third is to optimize anesthetic administration for faster recovery. Anesthetic depth monitoring can contribute to the reduction of the administered dose of anesthetics and improvement of the recovery profile.[9, 10]

Several devices for anesthetic depth monitoring, such as the bispectral index (BIS) monitor (Aspect Medical Systems, Inc., Norwood, MA), E-entropy monitor (GE Healthcare, Chicago, IL), and SedLine monitor (Mashimo, Irvine, CA), have been developed and are currently employed in clinical settings.[11] These devices are based on the analyses of electroencephalogram (EEG). The BIS monitor is representative of these monitors. BIS values range from 0 to 100; a value of 0 is equivalent to flat EEG activity, whereas a BIS value of 100 is equivalent to the completely awake condition.[11] The recommended target BIS value under general anesthesia ranges from 40 to 60.[11]

Recently, SmartPilot View (SPV; Dräger Medical, Lübeck, Germany), another type of anesthetic depth monitoring device, has been developed. Cirillo et al. reported the efficacy of SPV on the optimization of anesthetic administration in clinical settings.[12] SPV calculates the effect-site concentration of anesthetics based on pharmacokinetic/pharmacodynamic simulations, computes the pharmacodynamic interaction between hypnotics and opioids based on the calculated effect-site concentrations, and displays the noxious stimulation response index (NSRI).[13, 14] NSRI values range from 0 to 100. According to the SPV instruction manual, an NSRI of 50 under volatile anesthetic/opioid anesthesia is equivalent to the anesthetic depth at which 50% of patients are able to tolerate the noxious stimulation caused by skin incision (i.e., minimum alveolar concentration (MAC) 50), and an NSRI of 20 is equivalent to MAC 90 (Fig. 1). Under propofol/opioid anesthesia, an NSRI of 50 is equivalent to the anesthetic depth at which 50% of patients do not respond to the stimulation caused by laryngoscopy (i.e., tolerance of laryngoscopy (TOL) 50), and an NSRI of 20 is equivalent to TOL 90 (Fig. 1).[13] In addition, an NSRI of 90 is equivalent to the anesthetic depth at which 50% of patients can tolerate the stimulation caused by "shake and shout" (i.e., tolerance of shake and shout (TOSS) 50), and an NSRI of 70.5 is equivalent to TOSS 90 (Fig. 1).

Since the parameters evaluated by NSRI and BIS are completely different, we hypothesized that there might be possible clinical utility in simultaneous monitoring of NSRI and BIS for the optimization of anesthetic depth. However, if BIS can be predicted from NSRI with high accuracy, there might be no clinical significance for the simultaneous monitoring of NSRI and BIS. We, thus, conducted this pilot study to investigate the predictability of BIS from NSRI prior to performing clinical investigations for the evaluation of the efficacy of anesthetic management guided by simultaneous monitoring of NSRI and BIS.

Methods

Study population

Among adult patients scheduled for elective surgery under general anesthesia at our hospital from November 2015 to January 2017, a total of 40 patients were enrolled in this study.

According to the instruction manual of SPV, SPV was not indicated in the following patients: those over 90 years old; those with height of less than 150 cm or over 200 cm, body weight of less than 40 kg or more than 140 kg, body mass index of over 35 kg/m^2, and American Society of Anesthesiologists physical status IV or higher; and alcoholic patients. Additional exclusion criteria were pregnancy, central nervous system dysfunction, liver disorders, and renal disorders.

Data collections

The Apollo anesthesia workstation (Dräger Medical) equipped with SPV was used in all cases. Data of continuous administration of desflurane, propofol, and remifentanil are automatically integrated into the SPV, and data of bolus injections of propofol and fentanyl are manually entered. No premedication was administered in any of the patients. Prior to the induction of general anesthesia, standard monitoring (i.e., electrocardiogram, non-invasive blood pressure, and pulse oximetry) was applied. After tracheal intubation, a sensor for the BIS monitor was mounted on the forehead of each patient. All patients underwent surgery either under desflurane/opioid anesthesia (group D) or under propofol/opioid anesthesia (group P)

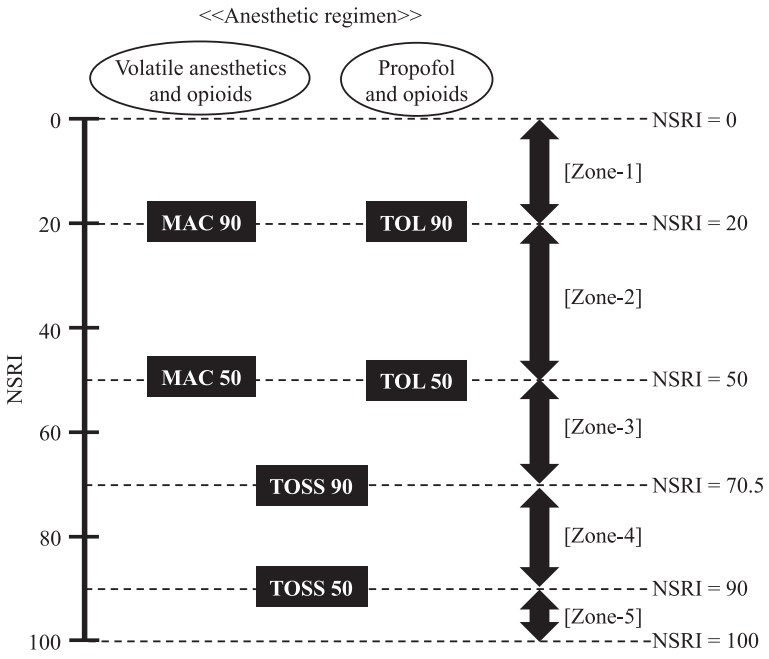

Fig. 1 Definitions of MAC 50, MAC 90, TOL 50, TOL 90, TOSS 50, and TOSS 90

NSRI values of 50 and 20 under volatile anesthetic/opioid anesthesia are equivalent to an anesthetic depth of MAC 50 and MAC 90, respectively. NSRI values of 50 and 20 under propofol/opioid anesthesia are equivalent to an anesthetic depth of TOL 50 and TOL 90, respectively. NSRI values of 90 and 70.5 under general anesthesia are equivalent to an anesthetic depth of TOSS 50 and TOSS 90, respectively. In this study, the range of NSRI was divided into five zones: zones 1, 2, 3, 4, and 5 were defined as NSRI values of 0–20, 21–50, 51–70, 71–90, and 91–100, respectively.

NSRI: noxious stimulation response index, MAC: minimum alveolar concentration, TOL: tolerance of laryngoscopy, TOSS: tolerance of shake and shout

without application of any kind of regional anesthesia. For the maintenance of general anesthesia, desflurane, fentanyl, and remifentanil were administered to patients in group D, and propofol, fentanyl, and remifentanil were administered to patients in group P. The attending anesthesiologist selected the anesthetic regimen (i.e., either desflurane/opioid anesthesia or propofol/opioid anesthesia) and decided the dose of anesthetics. For muscle relaxation, rocuronium was administered as determined by each attending anesthesiologist.

We divided the NSRI range into five zones from 1 to 5. Zones 1, 2, 3, 4, and 5 were defined as NSRI values of 0-20, 21-50, 51-70, 71-90, and 91-100, respectively (Fig. 1). Our study protocol did not specify the timing of data recording. During anesthetic management, the attending anesthesiologist arbitrarily recorded the BIS values once each when the NSRI value was in each zone for each patient. Simultaneously, blood pressure, heart rate, oxygen saturation in the peripheral artery, end-tidal concentration of carbon dioxide, effect-site concentration of remifentanil, and effect-site concentration of fentanyl were also recorded. The effect-site concentrations of desflurane in group D and those of propofol in group P at each measurement time point were also recorded.

Statistical analyses

Continuous data are expressed as means ± SD. After confirming homogeneity of variance using the Bartlett test, the unpaired t-test was used for inter-group comparisons of continuous data, the Dunnett test for comparisons of continuous data within each group, and the chi-squared test for comparisons of categorical data between the two groups. The predictability of BIS from NSRI was examined using linear regression analysis in each zone. Statistical significance was set to $P < 0.05$. We used JMP version

Table 1 Patient characteristics

	Group D (n = 20)	Group P (n = 20)
Gender (female/male)	13/7	15/5
Age (year)	54 ± 18	57 ± 20
Height (cm)	161.4 ± 7.8	160.6 ± 7.3
Weight (kg)	59.2 ± 11.2	58.7 ± 10.5
Body mass index (kg/m^2)	22.6 ± 3.5	22.8 ± 3.6
ASA-PS (I/II)	11/9	5/15
Surgical procedure		
Laparotomy	9	5
	Uterus: 6	Uterus: 3
	Ovary: 2	Ovary: 2
	Small intestine: 1	
Laparoscopic surgery	11	14
	Ovary: 3	Uterus: 1
	Gall bladder: 2	Ovary: 4
	Stomach: 3	Gall bladder: 4
	Colon/Rectum: 3	Stomach: 1
		Colon/Rectum: 2
		Inguinal hernia: 2
Thoracoscopic/laparoscopic surgery	0	1
		Esophagus: 1

ASA-PS: American Society of Anesthesiologists physical status

7.0.2 (SAS Institute, Cary, NC) for the statistical analyses.

Ethics approval

The study protocol was approved by the Ethics Committee of Toho University Sakura Medical Center (protocol No. 2015-041). We obtained written informed consent from all participating patients.

Results

Of the total of 40 patients enrolled in this study, 20 patients each were assigned to groups D and P, based on the anesthetic regimen selected by the attending anesthesiologist.

Table 1 presents the patients' characteristics. No significant differences in patient characteristics (i.e., gender, age, height, weight, body mass index, and American Society of Anesthesiologists physical status) were detected between the two groups. The surgical procedure for each patient is also presented in Table 1.

The vital signs during anesthesia in groups D and P are presented in Table 2. In all cases, there were no adverse circulatory and respiratory events during anesthesia management, and surgery was completed uneventfully. The drug concentrations during anesthesia management in groups D and P are presented in Table 3. In group D, the effect-site concentrations of desflurane when NSRI values were within zones 2, 3, 4, and 5 were significantly lower than when NSRI value was within zone 1 ($P < 0.0001$ for all comparisons, Dunnett test). In group D, the effect-site concentrations of remifentanil when NSRI values were within zones 2, 3, 4, and 5 were significantly lower than when NSRI value was within zone 1 ($P < 0.0001$ for all comparisons, Dunnett test). The effect-site concentrations of fentanyl in group D when NSRI values were within zones 3, 4, and 5 were significantly higher than those when NSRI value was within zone 1 ($P = 0.0204$, $= 0.0062$, and $= 0.0106$, respectively, Dunnett test). However, the effect-site concentrations of fentanyl in group D when NSRI value was within zone 2 were similar to those when NSRI value was within zone 1. The effect-site concentrations of propofol in group P when NSRI values were within zones 3, 4, and 5 were significantly lower than when NSRI value was within zone 1 ($P < 0.0001$ for all comparisons, Dunnett test); however, the effect-site concentrations of propofol in group P when NSRI value was within zone 2 were similar to those when NSRI value was within zone 1. The effect-site concentrations of remifentanil in group P when NSRI values were within zones 2, 3, 4, and 5 were significantly lower than when NSRI value was within zone 1 ($P < 0.0001$, < 0.0001, < 0.0001, and < 0.0001, respectively, Dunnett test). The effect-site concentrations of fentanyl in group P when

Table 2 Vital sign during anesthetic management

Group	Vital sign	Noxious stimulation response index				
		Zone 1	Zone 2	Zone 3	Zone 4	Zone 5
D	Blood pressure (mmHg)					
	Systolic	99 ± 21	102 ± 21	115 ± 20	119 ± 21	124 ± 22
	Diastolic	55 ± 15	57 ± 15	66 ± 15	68 ± 16	69 ± 15
	Heart rate (beats/min)	64 ± 18	67 ± 16	68 ± 14	69 ± 21	71 ± 23
	SpO_2 (%)	99 ± 1	100 ± 1	100 ± 1	100 ± 0	100 ± 0
	End-tidal concentration of carbon dioxide (mmHg)	35 ± 3	36 ± 3	36 ± 5	37 ± 5	38 ± 5
P	Blood pressure (mmHg)					
	Systolic	102 ± 14	105 ± 16	100 ± 19	113 ± 17	121 ± 20
	Diastolic	59 ± 13	59 ± 9	57 ± 11	63 ± 9	66 ± 12
	Heart rate (beats/min)	66 ± 11	66 ± 10	65 ± 10	61 ± 9	63 ± 10
	SpO_2 (%)	99 ± 1	99 ± 1	99 ± 1	100 ± 1	100 ± 1
	End-tidal concentration of carbon dioxide (mmHg)	34 ± 3	36 ± 4	36 ± 4	37 ± 5	46 ± 14

SpO_2: oxygen saturation of peripheral artery.

Table 3 Drug concentrations during anesthetic management

Group	Drug concentrations	Noxious stimulation response index				
		Zone 1	Zone 2	Zone 3	Zone 4	Zone 5
D	Effect site concentration of desflurane (%)	4.4 ± 0.5	3.8 ± 0.4 *	2.9 ± 0.4 *	2.2 ± 0.3 *	1.6 ± 0.3 *
	Effect site concentration of remifentanil (ng/mL)	2.9 ± 1.1	1.1 ± 0.6 *	0.5 ± 0.3 *	0.5 ± 0.3 *	0.4 ± 0.3 *
	Effect site concentration of fentanyl (ng/mL)	0.8 ± 0.7	0.7 ± 0.7	1.4 ± 0.6 *	1.5 ± 0.5 *	1.4 ± 0.5 *
P	Effect site concentration of propofol (μg/mL)	3.1 ± 0.5	3.0 ± 0.5	2.2 ± 0.5 *	1.5 ± 0.3 *	0.9 ± 0.2 *
	Effect site concentration of remifentanil (ng/mL)	3.6 ± 1.1	2.6 ± 0.7 *	1.6 ± 0.5 *	0.8 ± 0.4 *	0.4 ± 0.2 *
	Effect site concentration of fentanyl (ng/mL)	1.9 ± 0.6	0.7 ± 0.7 *	0.9 ± 1.0 *	1.3 ± 0.5 *	1.3 ± 0.3 *

*: $P < 0.05$ versus the data in same group when noxious stimulation response index was within zone-1, Dunnett test.

NSRI values were within zones 2, 3, 4, and 5 were significantly lower than when NSRI value was within zone 1 ($P < 0.0001$, < 0.0001, $= 0.0260$ and $= 0.0214$, respectively, Dunnett test).

The entire data of NSRI and BIS in group D are presented in Fig. 2a. The results of linear regression analysis in each zone in group D are presented in Table 4. The P values of regression coefficient in zones 1, 2, 4, and 5 were over 0.05. Although the P value of regression coefficient in zone 3 was less than 0.05, the R^2 value of the prediction formula in zone 3 was 0.4434. Fig. 2b presents the residual plot in group D. Residual was calculated using the following equation:

[Residual] = [Measured BIS] − [Predicted BIS]

Fig. 2c presents the distribution of BIS values when NSRI value was within zone 1. In 10 patients, BIS value was less than 40 when NSRI value was within zone 1. Fig. 2d presents the distribution of BIS values when NSRI values were within zones 4 and 5. In 10 patients, BIS value was 60 or less when NSRI value was within zone 4, whereas BIS value was 60 or less when NSRI value was within zone 5 in seven patients.

The entire data of NSRI and BIS in group P are presented in Fig. 3a. The results of linear regression analysis in each zone in group P are presented in Table 4. The P values of regression coefficient were over 0.05 in all zones. Fig. 3b presents the residual plot in group P. Residual was calculated using the equation described above. Fig. 3c presents the distribution of BIS values when NSRI value was within zone 1. In 16 patients, BIS value was less than 40 when NSRI value was within zone 1. Fig. 3d presents the distribution of BIS values when NSRI values were within zones 4 and 5. In 16 patients, BIS value was 60 or less when NSRI value was within zone 4, whereas BIS value was 60 or less when NSRI value was within zone 5 in six patients.

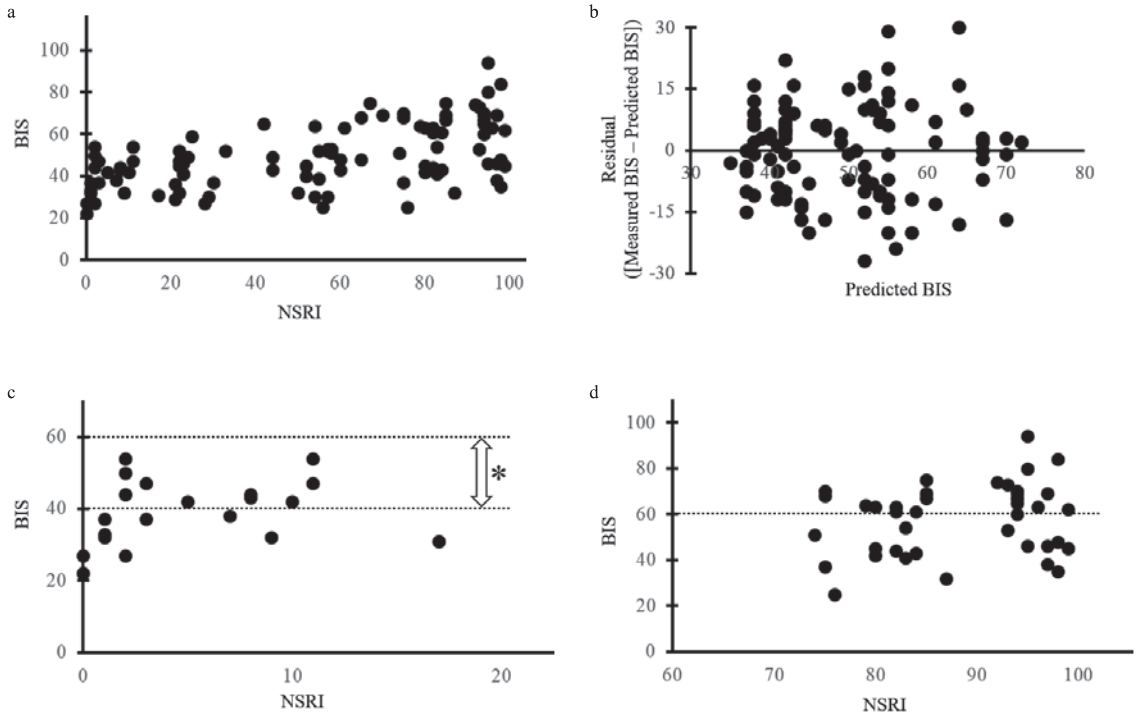

Fig. 2 The predictability of BIS from NSRI in patients under desflurane/opioid anesthesia
a: The entire data of NSRI and BIS in group D are presented. b: Considering that the recommended target BIS value during general anesthesia management ranges from 40 to 60, the distribution of the residuals suggested that it is inappropriate to predict BIS from NSRI. c: BIS value was less than 40 when NSRI value was within zone 1 in 10 patients. d: BIS value was 60 or less when NSRI value was within zone 4 in 10 patients, and BIS value was 60 or less when NSRI value was within zone 5 in seven patients.
NSRI: noxious stimulation response index, BIS: bispectral index, *: recommended target BIS value under general anesthesia, which ranges from 40 to 60.

Table 4 Results of linear regression analysis

Group	Zone	Prediction formula	P value	R^2 value
D	1	[Predicted BIS] = 36.83 + 0.4507 × [Observed NSRI]	0.3217	0.0545
	2	[Predicted BIS] = 32.87 + 0.4001 × [Observed NSRI]	0.1843	0.0958
	3	[Predicted BIS] = −53.53 + 1.763 × [Observed NSRI]	0.0014	0.4434
	4	[Predicted BIS] = 23.97 + 0.3685 × [Observed NSRI]	0.6668	0.0105
	5	[Predicted BIS] = 339.2 − 2.899 × [Observed NSRI]	0.0850	0.1558
P	1	[Predicted BIS] = 33.86 + 0.1894 × [Observed NSRI]	0.5753	0.0178
	2	[Predicted BIS] = 38.33 + 0.0717 × [Observed NSRI]	0.8201	0.0029
	3	[Predicted BIS] = 63.73 − 0.2862 × [Observed NSRI]	0.5082	0.0247
	4	[Predicted BIS] = 102.0 − 0.6610 × [Observed NSRI]	0.4638	0.0302
	5	[Predicted BIS] = 208.1 − 1.567 × [Observed NSRI]	0.2271	0.0799

BIS: Bispectral Index, NSRI: noxious stimulation response index.

Discussion

In this study, we examined the predictability of BIS from NSRI using linear regression analysis. In group D, the P value of regression coefficient was less than 0.05 in zone 3 only. However, even in zone 3, the R^2 value of the prediction formula was not sufficiently high. Considering that the recommended target BIS value during general anesthesia ranges from 40 to 60, the distribution of the residuals in group D was too wide. These results suggest that it is inappropriate to predict BIS from NSRI in clinical practice in patients under desflurane/opioid anesthesia. In

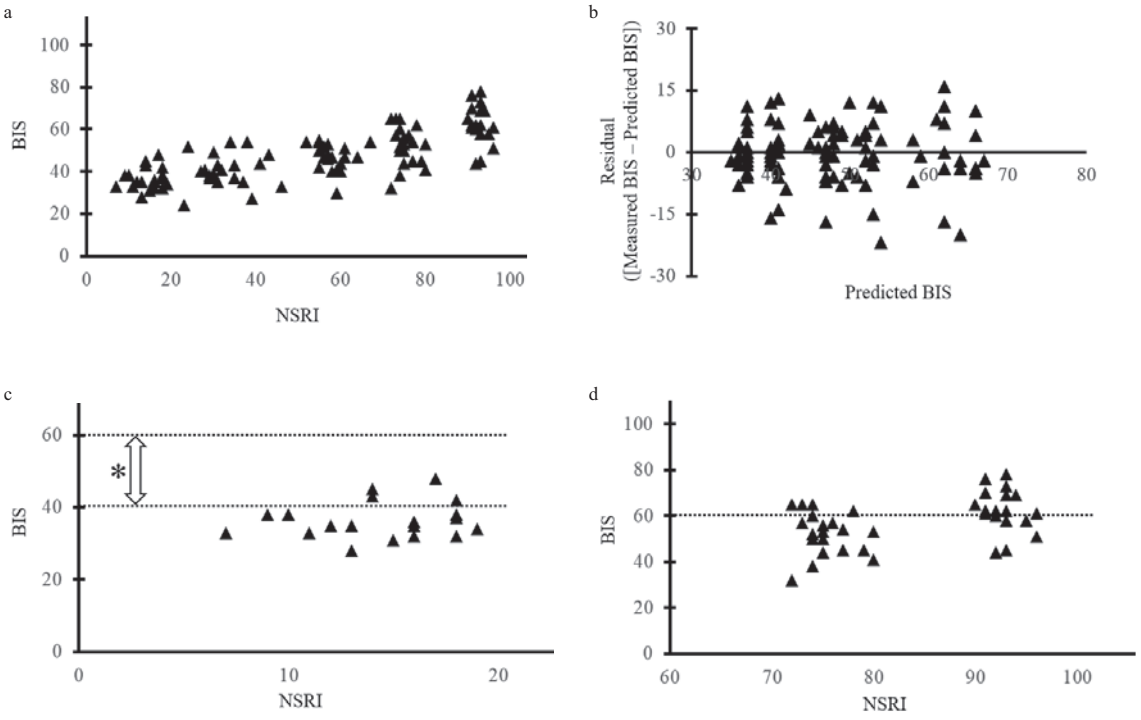

Fig. 3 The predictability of BIS from NSRI in patients under propofol/opioid anesthesia
a: The entire data of NSRI and BIS in group P are presented. b: Considering that the recommended target BIS value under general anesthesia ranges from 40 to 60, the distribution of the residuals suggested that it is inappropriate to predict BIS from NSRI. c: BIS value was less than 40 when NSRI value was within zone 1 in 16 patients. d: BIS value was 60 or less when NSRI value was within zone 4 in 16 patients, and BIS value was 60 or less when NSRI value was within zone 5 in six patients.
NSRI: noxious stimulation response index, BIS: bispectral index, *: recommended target BIS value under general anesthesia, which ranges from 40 to 60.

group P, the P values of regression coefficient were over 0.05 in all zones. Again, considering that the recommended target BIS value during general anesthesia ranges from 40 to 60, the distribution of the residuals in group P was not within the acceptable range. These results indicate that it is also inappropriate to predict BIS from NSRI in clinical practice in patients under propofol/opioid anesthesia.

The BIS monitor is one of the devices used for anesthetic depth monitoring that is based on EEG analyses. The EEG changes along with the level of consciousness.[15] It is, thus, reasonable to consider that BIS mainly reflects the hypnotic levels. NSRI is an index computed from the pharmacodynamic interaction between hypnotics and analgesics. That is, evaluation of the anesthetic depth by NSRI reflects the level of both hypnosis and analgesia. We suppose that prediction of BIS from NSRI is difficult due to the different parameters for the evaluation of anesthetic depth, although both BIS and NSRI are utilized as indices for anesthetic depth monitoring in clinical settings.

Although AAGA is a rare complication related to surgery under general anesthesia with an incidence rate of 0.11%-0.7%,[16–20] it might result in long-lasting adverse psychological effects.[2] Thus, prevention of AAGA has been one of the biggest concerns for anesthesiologists as well as patients undergoing surgery. Two clinical studies reported that the use of the BIS monitor significantly reduced the incidence of AAGA; however, total prevention of AAGA could not be achieved.[21, 22] When not using specific devices for anesthetic depth monitoring, measurement of end-tidal anesthetic-agent concentration (ETAC) is the alternative method for preventing AAGA during volatile anesthetic/opioid anesthesia. Clinical studies that compared the preventive effects on AAGA between BIS- and ETAC-guided anesthesia reported no significant differences in the outcomes.[23, 24] In addition, several factors are known to affect the BIS monitor, leading to inappropriate evaluation of the anesthetic depth under specific conditions.[25] Anesthetics may cause paradoxical changes in BIS;

electric devices interfere with the BIS monitor; some kinds of clinical conditions, such as hypoglycemia and cerebral ischemia, modify BIS; and contamination of the EEG by the electromyogram (EMG) might result in misanalysis.[25] Hagihira et al. reported two cases in which BIS paradoxically decreased to less than 30 during the awakening process from general anesthesia due to misanalysis of the EEG waveform pattern.[26]

In this study, the data recorded when NSRI values were within zones 1, 2, 3, 4, and 5 were not all recorded in chronological order. It is, therefore, inappropriate to examine changes in continuous data within groups using one-way repeated-measures analysis of variance. We, thus, applied the Dunnett test to compare continuous data when NSRI values were within zones 2, 3, 4, and 5 with those when NSRI value was within zone 1. There was a different tendency in the effect-site concentrations of fentanyl between the two groups. We suppose that this result reflects the impact of bolus administration on the effect-site concentration of fentanyl. The effect-site concentrations of desflurane and remifentanil in group D when NSRI values were within zones 3, 4, and 5 were significantly lower than those when NSRI value was within zone 1. Similarly, the effect-site concentrations of propofol and remifentanil in group P when NSRI values were within zones 3, 4, and 5 were significantly lower than those when NSRI value was within zone 1. Both the raw data of the effect-site concentrations of anesthetics and the results of statistical analyses suggested that the time points of BIS recording when NSRI values were within zones 3, 4, and 5 were either near the end of surgery or during the awakening process from general anesthesia. We confirmed this by retrospective inspection of anesthetic records. As presented in Fig. 2d and Fig. 3d, BIS value was 60 or less when NSRI value ranged from 71 to 100 in many patients under both desflurane/opioid anesthesia and propofol/opioid anesthesia. We suppose that these results might suggest the superiority of NSRI to BIS for anesthetic depth monitoring near the end of surgery and during the awakening process from general anesthesia.

During anesthesia management, adverse sequelae related to excessively deep anesthesia, such as circulatory suppression, should be prevented. Furthermore, there might be a correlation between deep anesthesia and postoperative cognitive disorders.[7, 8] As presented in Fig. 2c and Fig. 3c, BIS value was less than 40 when NSRI values ranged from 0 to 20 in many patients under both desflurane/opioid anesthesia and propofol/opioid anesthesia, suggesting that the anesthetic depth might be excessively deep in these patients at this time point. Based on these results, we suppose that anesthetic management guided by both NSRI and BIS might contribute to the maintenance of appropriate anesthetic depth and prevention of excessively deep anesthesia.

In the recent studies investigating the clinical efficacy of NSRI as an anesthetic depth index, Morimoto et al. maintained NSRI values from 0 to 20 throughout the anesthetic management, whereas Leblanc et al. maintained NSRI values from 0 to 20 at the time of tracheal intubation and surgical incision and from 20 to 50 during the rest of surgery.[14, 27] We consider that the recommended range of NSRI during surgery should be elucidated by future investigations.

Limitations

This study has some limitations. First, the number of patients enrolled in this study was small. Second, this study involved only a single center. Third, the attending anesthesiologist selected the anesthetic regimen. Thus, this study was not conducted in a blinded manner. Fourth, the attending anesthesiologist arbitrarily recorded the data in this study, because the study protocol did not specify the timing of data recording. Fifth, there was no regulation of neuromuscular blockade in this study protocol, and rocuronium administration was based on the decision of each attending anesthesiologist. An increase in muscle tone around the BIS sensor increases the BIS value (i.e., electromyogram interference), whereas BIS can be decreased by excessive administration of muscle relaxants.[11, 25] Therefore, we cannot neglect these possible effects on the measured BIS values in this study. These issues should be resolved by conducting further clinical investigations to evaluate the efficacy of anesthetic management guided by simultaneous monitoring of NSRI and BIS.

Conclusions

The results of this study indicate that it is inappropriate to predict BIS from NSRI during general anesthesia management in clinical practice. In addition, a BIS value of 60 or less was observed in many patients when NSRI values ranged from 71 to 100, and a BIS value of less than 40 was observed in many patients when NSRI values ranged from 0 to 20. These observed discrepancies in anesthetic depth evaluation between NSRI and BIS might suggest the clinical utility of simultaneous monitoring of NSRI and BIS for the maintenance of appropriate anesthetic depth, which

would also possibly contribute to the prevention of excessively deep anesthesia and AAGA.

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Authors' contribution: MU, KK, and TK designed and conducted the study, analyzed the data, drafted the manuscript and prepared figures and tables. HK, RK and KS conducted the study, and helped to analyze the data and edit the manuscript. All authors read and approved the final manuscript.

Ethics statement: The study protocol was approved by the Ethics Committee of Toho University Sakura Medical Center (No. 2015-041). All patients provided their written informed consent to participate in this study.

Conflicts of interest: None declared.

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