Received: 17 August 2022 | Accepted: 1 September 2022

DOI: 10.1111/1759-7714.14658

ORIGINAL ARTICLE

WILEY

The utility of bispectral index monitoring in flexible bronchoscopy: A single-center, retrospective observational study

Jun Yamada[1] | Daisuke Hazama[1] | Motoko Tachihara[1] | Yuki Kawanami[2] | Aki Kawaguchi[1] | Atsuhiko Yatani[1] | Hiroki Sato[1] | Chihiro Mimura[1] | Naoko Katsurada[1] | Masatsugu Yamamoto[1] | Yoshihiro Nishimura[1] | Kazuyuki Kobayashi[1]

[1]Division of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan

[2]Department of Clinical Engineering, Kobe University Hospital, Kobe, Japan

Correspondence
Motoko Tachihara, Department of Respiratory Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan.
Email: mt0318@med.kobe-u.ac.jp

Abstract

Background: The desired depth of sedation during flexible bronchoscopy is one in which verbal contact is possible whenever necessary. Although it is common that the depth of sedation is assessed by validated instruments such as the modified observer's assessment of alertness and sedation (MOAA/S) score, the repeated stimulation associated with the assessment can affect the sedation. The bispectral index (BIS) has been widely used for general anesthesia due to its objective and noninvasive nature. However, the utility of BIS monitoring and a target BIS value for use during bronchoscopy have not been fully elucidated.

Methods: We performed a retrospective observational study to assess the utility of the BIS value for monitoring conscious sedation during bronchoscopy at Kobe University Hospital from August 2020 to April 2021.

Results: Eighteen patients underwent bronchoscopy with BIS monitoring. The BIS value significantly correlated with the MOAA/S score ($r = 0.2$, $p < 0.01$), and the correlation was stronger in sufficiently sedated patients ($r = 0.486$, $p < 0.01$). The lowest MOAA/S score during the procedure was highly correlated with the BIS value ($r = 0.625$, $p < 0.01$). The BIS monitoring seemed to be more sensitive to changes in the sedation level than the MOAA/S score, heart rate and mean arterial pressure. The median BIS value at an MOAA/S score of 3–4, the desired depth of sedation, was 82.0.

Conclusions: BIS value is useful for monitoring sedation during bronchoscopy. This study suggests that a BIS value of 82 reflects an adequate level of sedation.

KEYWORDS
BIS value, flexible bronchoscopy, MOAA/S score, sedation

INTRODUCTION

Flexible bronchoscopy (FB) is widely used for the diagnosis and treatment of lung and airway diseases. The British Thoracic Society (BTS) guidelines on diagnostic FB[1] recommends intravenous sedation to promote tolerance, ease of procedure and willingness to undergo a re-examination if needed. Sedation is divided into four levels: minimal sedation, moderate sedation, deep sedation, and general anesthesia.[2] The guideline states that the desired depth of sedation is moderate sedation, in which patients can respond purposefully to verbal commands. The depth of sedation during FB is conventionally assessed by the patient response to stimulation using clinical sedation scales such as the Ramsay sedation score (RSS),[3] Richmond agitation-sedation scale (RASS),[4] observer's assessment of alertness/sedation (OAA/S) score,[5] and modified observer's assessment of alertness and sedation (MOAA/S) score.[6] However,

repeated stimulation of the patient to assess the score can affect the sedation itself. Therefore, objective and noninvasive monitoring tools for patients under conscious sedation are eagerly anticipated. The bispectral index (BIS), a parameter calculated based on electroencephalographic (EEG) analysis expressed as a score between 0 (isoelectric EEG) and 100 (awake), has been widely used for monitoring general anesthesia[7–9] and has been reported to be useful in gastrointestinal endoscopy.[10,11] Recently, several reports demonstrated that BIS is useful for monitoring sedation in FB. Fruchter et al. reported that complications and propofol dose during FB were comparable between the BIS-guided group and the OAA/S-guided group.[5] Quesada et al. showed that, compared with the MOAA/S score, BIS monitoring reduced complications and the propofol dose in patients undergoing sedation for endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).[6] However, there are few data about the correlation between clinical sedation scores and BIS values and target BIS values during FB. To clarify these points, we conducted this retrospective observational study.

METHODS

Study design and subjects

This was a single-center, retrospective, observational study to assess the utility of BIS monitoring for conscious sedation during FB at Kobe University Hospital. All patients who underwent FB with BIS monitoring between August 2020 and April 2021 were reviewed. The study was approved on September 27, 2021, by the Institutional Ethics Committee of the Kobe University Hospital. A waiver of consent was granted due to the retrospective design and the confirmed minimal risk to the patients. Instead, the research content was posted on the hospital website. The study conformed with the Helsinki Declaration.

Procedure

FB was performed by experienced pulmonologists, while sedation was performed by a nonanesthesiologist. The level of sedation was assessed using the MOAA/S score, which ranges from 0 to 6 (Table 1).[12] Depth of sedation with the MOAA/S score was defined as follows: ≥5, minimal sedation; 3–4, moderate sedation; ≤2, deep sedation. Before the procedure, the pharynx was locally anesthetized with a 4% lidocaine spray (5 ml) after 2% viscous lidocaine solution (6 ml) was retained in the mouth without swallowing for 5 min. Sedation was started with intravenous injection of midazolam (2 mg) 3 min before the insertion of the bronchoscope. Additional midazolam (1 mg) was given at intervals of 4 min or more when the operator determined necessary based on the MOAA/S score, blood pressure and heart rate (HR). If the patient was older than 75 years or weighed less than 45 kg, the initial dose of midazolam was reduced to 1 mg. For some patients, pethidine (17.5 mg) or fentanyl (10–20 μg) was administered in combination with the initial midazolam injection to facilitate the procedure and promote comfort. When we used fentanyl, additional fentanyl (10 μg) and midazolam (1 mg) with an interval of 4 min or more were given as needed. After insertion of the bronchoscope, topical anesthesia of the upper airway with 2% lidocaine was administered through the working channel.

TABLE 1 Modified observer's assessment of alertness and sedation (MOAA/S) score

Responsiveness	Score
Agitated	6
Responds readily to name spoken in normal tone ("alert")	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

BIS monitoring

During the procedure, a disposable BIS sensor (BIS Quatro sensor; Nihon Kohden) was placed on the patient's forehead and connected to a BIS monitoring system (Life Scope TR, BSM-6301; Nihon Kohden) according to the manufacturer's instructions. This system converts the EEG parameters into BIS value, which is shown on the monitor in the bronchoscopy room with vital signs. BIS values were recorded every 2.5 min.

Data collection and study definitions

We also recorded the following: demographic characteristics, cumulative doses of midazolam, MOAA/S score at any given time, vital signs every 2.5 min, and procedural complications. Complications were defined as (1) respiratory failure requiring intubation, (2) hemoptysis, (3) SpO_2 < 88% despite bag mask ventilation, (4) arrhythmia requiring cardioversion or an antiarrhythmic agent, (5) hypotension: mean arterial pressure (MAP) < 60 mmHg, (6) pneumothorax, (7) intolerance of the procedure or (8) death. Hepatic impairment was defined as an elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin above upper limit of normal. Renal impairment was defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min.

Statistical analysis

The statistical analyses were performed in EZR software, version 1.51 (Saitama Medical Center, Jichi Medical

University, Saitama, Japan).[13] Quantitative variables are expressed as the mean and standard deviation (SD) or median and interquartile range as appropriate. We described categoric variables as frequencies and percentages. Spearman's rank correlation coefficient was used between the MOAA/S score and BIS value at the nearest time. The Wilcoxon rank-sum test was used to compare the BIS value, MOAA/S score, HR and MAP for each three different moments of the procedure (T1; beginning of the procedure, T2; biopsy, T3; end of the procedure). The Mann–Whitney U test was used to compare BIS values for each MOAA/S score, and to compare the lowest BIS value during the procedure for each age, gender, weight, midazolam dosage, hepatic impairment, and renal impairment. Receiver operating characteristic (ROC) curve analysis was used to evaluate the discriminating performance of the BIS. Statistical significance was set at a p-value of <0.05.

TABLE 2 Patient baseline characteristics

N	18
Age, years (mean ± SD)	58.9 ± 15.0
Gender	
Male	11 (61.1%)
Female	7 (38.9%)
Bodyweight (kg, median [range])	60 (58–64)
Hepatic impairment	4 (22.2%)
Renal impairment	2 (11.1%)
Procedure	
GS-TBB	7 (38.9%)
EBUS-TBNA	8 (44.4%)
BAL/TBLB	3 (16.7%)
Sedatives/opioids	
Midazolam alone	11 (61.1%)
Midazolam and pethidine combined	4 (22.2%)
Midazolam and fentanyl combined	3 (16.7%)
Dosage of midazolam, mg (mean ± SD)	3.88 ± 1.45

Abbreviations: BAL/TBLB, bronchoalveolar lavage/transbronchial lung biopsy; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; GS-TBB, guide sheath-transbronchial biopsy; SD, standard deviation.

RESULTS

Eighteen patients were enrolled in this study. The baseline characteristics of the patients are shown in Table 2. Of the total patients, seven patients underwent guide sheath-transbronchial biopsy (GS-TBB), eight underwent EBUS-TBNA, and three underwent bronchoalveolar lavage/transbronchial lung biopsy (BAL/TBLB). As sedative and analgesic agents, 11 patients received midazolam alone, four received midazolam and pethidine, and three received midazolam and fentanyl. The mean dosage of midazolam was 3.88 ± 1.45 mg. The lowest BIS value during the procedure was not significantly affected by age, gender, bodyweight, dosage of midazolam, or hepatic or renal impairment (Table 3). There were no complications in this study.

We first evaluated the correlation between the BIS value and the MOAA/S score. The BIS value during the procedure was significantly correlated with the MOAA/S score

TABLE 3 The lowest BIS value during the procedure

		N	Lowest BIS value (median [range])	p-value
Age				
	<70 years old	12	77 (70–80.25)	
	≥70 years old	6	75 (68.25–75.75)	0.347
Gender				
	Male	11	75 (69.5–77)	
	Female	7	77 (72.5–80.5)	0.413
Bodyweight				
	<50 kg	2	78 (76.5–79.5)	
	≥50 kg	15	75 (69.5–77)	0.41
Dosage of midazolam/bodyweight				
	<0.05 mg/kg	6	72.5 (70–76.5)	
	≥0.05 mg/kg	11	76 (70–78.5)	0.579
Hepatic impairment				
	Yes	4	79.5 (76.5–82)	
	No	14	71 (69–77)	0.0609
Renal impairment				
	Yes	2	72.75 (70.5–75)	
	No	16	76.5 (70–80.25)	0.323

Abbreviation: BIS, bispectral index.

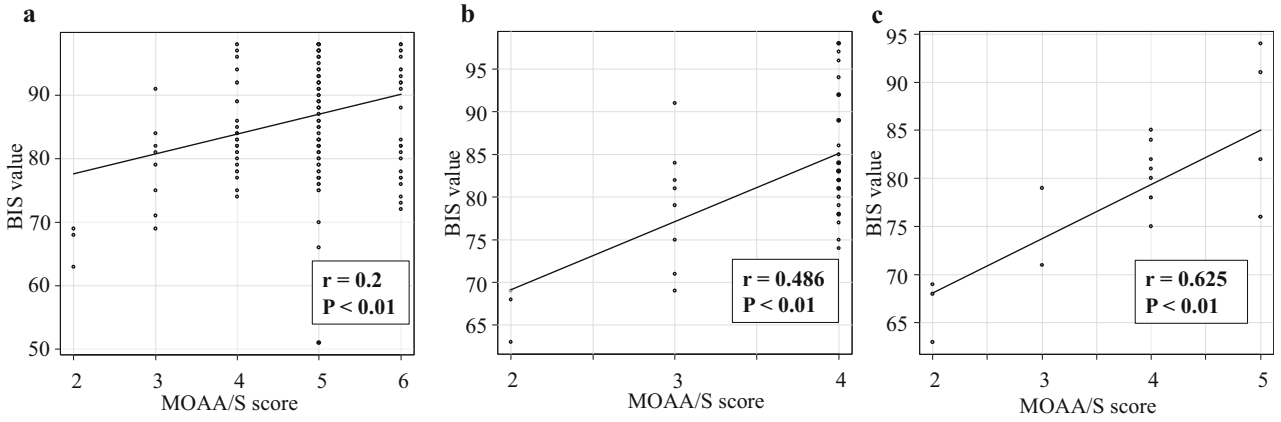

FIGURE 1 Correlation between the BIS value and the modified observer's assessment of alertness and sedation score (MOAA/S) (a), MOAA/S score ≤4 (b), and the lowest MOAA/S score during the procedure (c) at the nearest time. The correlation was calculated by Spearman's rank correlation coefficient. "*r*" denotes the correlation coefficient. A *p*-value <0.05 was considered significant

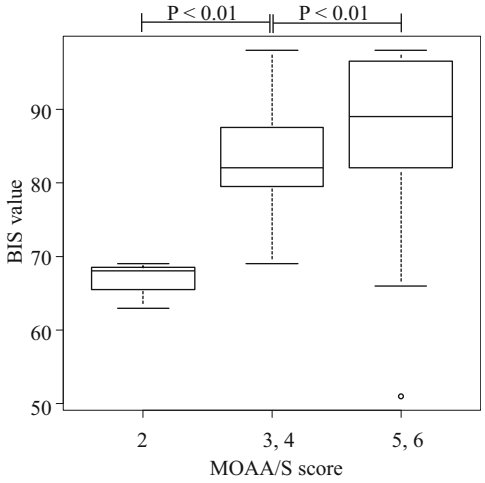

FIGURE 2 Distribution of BIS values for each MOAA/S score. *p*-values were calculated by the Mann–Whitney U test. A *p* value <0.05 was considered significant

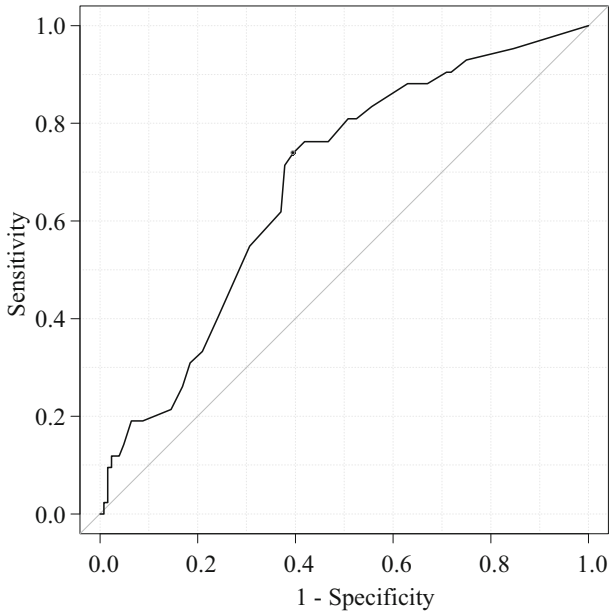

FIGURE 3 The receiver operating characteristic (ROC) curve for the BIS at sufficient sedation based on the MOAA/S score. The area under the receiver operating characteristic (ROC) curve was 0.676 (95% confidence interval [CI]: 0.586 to 0.766)

($r = 0.2$, $p < 0.01$; Figure 1(a)) and was significantly better correlated in sufficiently sedated patients (MOAA/S score ≤4) ($r = 0.486$, $p < 0.01$; Figure 1(b)). Moreover, a strong correlation was observed between the lowest MOAA/S score during the procedure and the BIS value ($r = 0.625$, $p < 0.01$; Figure 1(c)). These results indicate that the BIS value reflects the depth of sedation during FB.

We next sought to find the BIS value that corresponds to the adequate level of sedation in FB. The BIS values significantly changed with the increase in the level of sedation across the categorized MOAA/S scores (Figure 2). The median BIS values for MOAA/S scores of ≤2, 3–4, and ≥5 were 68.0 (65.5–68.5), 82.0 (79.5–87.5) and 89.0 (81.0–96.25), respectively (Table 4). The ROC curve for the BIS in

TABLE 4 The median BIS value for each MOAA/S score during the procedure

MOAA/S score	2	3, 4	5, 6
BIS value (median [range])	68.0 (65.5–68.5)	82.0 (79.5–87.5)	89.0 (81.0–96.25)
N	3	39	124

Abbreviations: BIS, bispectral index; MOAA/S, modified observer's assessment of alertness and sedation score.

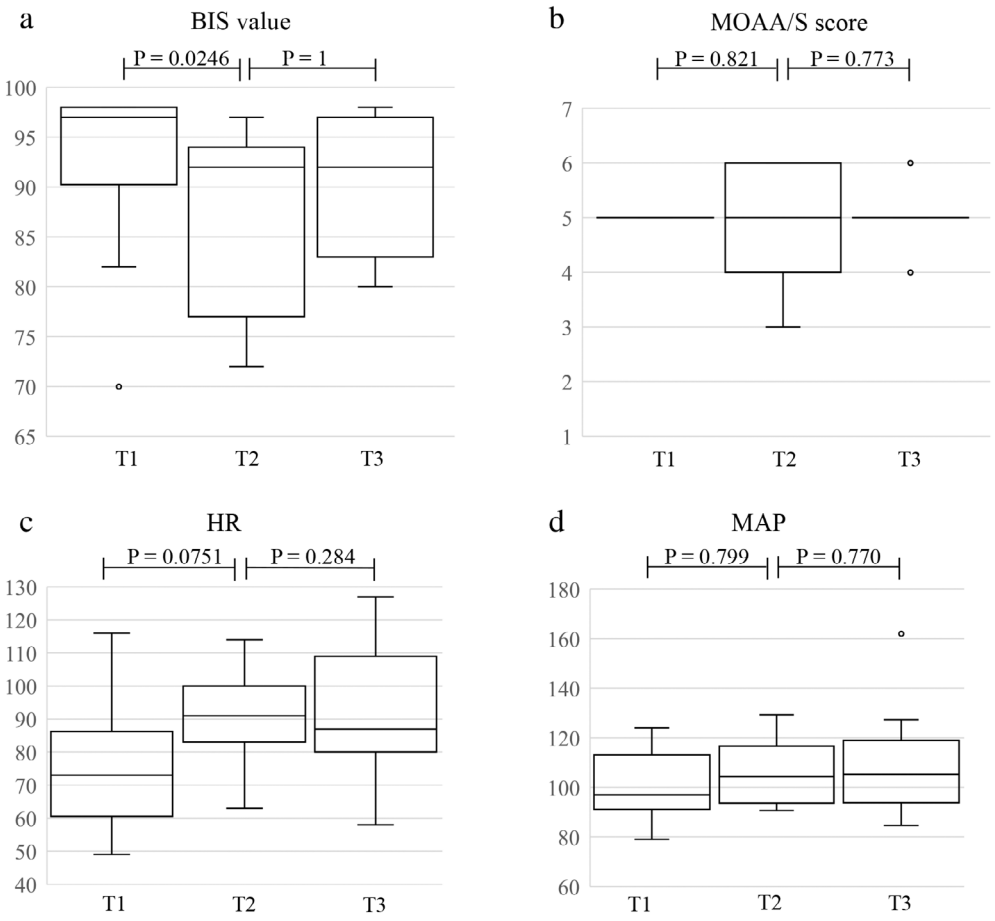

FIGURE 4 Boxplot of the median bispectral index (BIS) value (a), MOAA/S score (b), HR (c) and MAP (d) at each time point during the procedure. *p*-values were calculated by the Wilcoxon rank-sum test. A *p*-value <0.05 was considered significant. Abbreviations: T1, beginning of the procedure; T2, biopsy; T3, end of the procedure

predicting sufficient sedation (MOAA/S score ≤4) revealed that the area under the curve (AUC) was 0.676 (95% confidence interval [CI]: 0.586 to 0.766; Figure 3).

Finally, we compared the sensitivity of the BIS value and MOAA/S score to assess the depth of sedation during the procedure. A significant difference was detected in the BIS value between T1 and T2 (97 [92.5–98] at T1 vs. 92 [84–93.5] at T2, $p = 0.0246$; Figure 4(a)). In contrast, there was no significant difference in MOAA/S score (Figure 4(b)), HR (Figure 4(c)) or MAP (Figure 4(d)) between these two time points (MOAA/S score; 5 [5] at T1 vs. 5 [4.5–6] at T2, $p = 0.821$. HR; 73 [61–85] at T1 vs. 91 [84.5–96.5] at T2, $p = 0.0751$. MAP; 97 [91.7–113] at T1 vs. 104.3 [97.5–114.5] at T2, $p = 0.799$). These results suggest that BIS monitoring might be a more sensitive indicator than the MOAA/S score, HR and MAP.

DISCUSSION

We demonstrated the utility of BIS monitoring for assessing the level of sedation in patients undergoing FB. In accordance with previous reports,[4,10,14] the BIS value correlated with the clinically observed sedation scales. In this study, the correlation was stronger in patients under sufficient sedation (MOAA/S ≤ 4) than in all patients. Moreover, the lowest MOAA/S score during the procedure was strongly correlated with the BIS value. The BIS value was reported to be affected by the electromyogram (EMG) and increased during painful procedures[15] because the EMG frequencies overlap the relative beta ratio, a subparameter of BIS, in the 30–47 Hz range.[16] Therefore, insufficient sedation might induce movement-related EMG activity, which would falsely increase the BIS value and weaken its correlation with the MOAA/S score.

In the present study, a BIS value near 82 corresponded to adequate sedation levels for FB (MOAA/S score of 3–4). There is no consensus on the optimal BIS value during FB, whereas a target range of 65–85 has been recommended for sedation.[16] Several studies have compared sedation during FB using BIS versus clinical sedation scales. In the study by Fruchter et al., the sedation levels were targeted to achieve a BIS of 70–85 and an OAA/S of 2–4,[5] while Quesada et al. set a BIS of 60–80 and a MOAA/S of 2–3.[6] These target BIS values seem to be lower than the value we found in this study. However, a level of sedation where patients remain responsive to verbal commands (MOAA/S; 3–4) has been advocated during FB because we need patient cooperation when changing the patient's position or checking for pain during a biopsy. We thus believe the target BIS value of 82 is reasonable during FB.

Our data showed that the BIS value seemed to be more sensitive to changes in sedation level than the MOAA/S

score and vital signs. Several reports have previously compared the changes due to stimulation in these parameters. Andrzejowski et al. observed changes in the BIS and MOAA/S score after receiving intravenous epinephrine during general anesthesia. Comparing the values before and after the epinephrine injection, all patients showed an increase in BIS, while 25% of patients showed no increase in MOAA/S scores.[17] In another study, BIS monitoring was reported to be more sensitive to painful stimulation (endotracheal suctioning or repositioning) than vital signs, including HR and MAP, in intubated patients after cardiac surgery.[18] It is very important to maintain an adequate level of sedation since it should be deep enough to improve patient tolerance but not too deep to prevent serious complications. BIS monitoring is thus a valid monitoring tool for assessing the level of sedation in terms of sensitivity.

This study has several limitations. First, it was a retrospective single-center study with a small sample size. Second, sedation was performed by a different nonanesthesiologist, which might have affected the MOAA/S score due to its subjective nature. Third, the MOAA/S scores were not recorded at regular intervals. Therefore, the number of data points differed among patients. To confirm the usefulness of BIS monitoring in FB, in an ongoing prospective phase III study (jRCTs051210131) of the effect of midazolam with fentanyl on sedation in FB, we recorded the MOAA/S scores at regular intervals while simultaneously measuring BIS value.

In conclusion, the BIS value is useful to assess sedation during FB, and sedation with a BIS value of near 82 might be an option for proper sedation.

AUTHOR CONTRIBUTIONS

JY, DH, MT, YK, AK, AY, HS, CM, NK, and MY acquired the data. JY collected the data. JY, DH, and MT designed the study, analyzed the data and wrote the article. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to the participating patients for their cooperation in conducting this study.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ORCID

Jun Yamada https://orcid.org/0000-0002-7595-5843
Daisuke Hazama https://orcid.org/0000-0002-7854-3692
Motoko Tachihara https://orcid.org/0000-0002-4598-220X
Masatsugu Yamamoto https://orcid.org/0000-0003-0596-555X

REFERENCES

1. Du Rand IA, Blaikley J, Booton R, et al. British thoracic society guideline for diagnostic flexible bronchoscopy in adults. Respiration. 2013; 92:166–75.
2. Wahidi MM, Herth F, Yasufuku K, Shepherd RW, Yarmus L, Chawla M, et al. Technical aspects of endobronchial ultrasound-guided transbronchial needle aspiration: CHEST guideline and expert panel report. Chest. 2016;149:816–35.
3. José RJ, Shaefi S, Navani N. Sedation for flexible bronchoscopy: current and emerging evidence. Eur Respir Rev. 2013;22:106–16.
4. Zheng J, Gao Y, Xu X, Kang K, Liu H, Wang H, et al. Correlation of bispectral index and Richmond agitation sedation scale for evaluating sedation depth: a retrospective study. J Thorac Dis. 2018; 10:190–5.
5. Fruchter O, Tirosh M, Carmi U, Rosengarten D, Kramer MR. Prospective randomized trial of bispectral index monitoring of sedation depth during flexible bronchoscopy. Respiration. 2014;87:388–93.
6. Quesada N, Júdez D, Martínez Ubieto J, Pascual A, Chacón E, de Pablo F, et al. Bispectral index monitoring reduces the dosage of propofol and adverse events in sedation for endobronchial ultrasound. Respiration. 2016;92:166–75.
7. Johansen JW. Update on bispectral index monitoring. Best Pract Res Clin Anaesthesiol. 2006;20:81–99.
8. Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. Cochrane Database Syst Rev. 2014;2014:CD003843.
9. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology. 1997;86:836–47.
10. Bower AL, Ripepi A, Dilger J, Boparai N, Brody FJ, Ponsky JL. Bispectral index monitoring of sedation during endoscopy. Gastrointest Endosc. 2000;52:192–6.
11. Wehrmann T, Grotkamp J, Stergiou N, Riphaus A, Kluge A, Lembcke B, et al. Electroencephalogram monitoring facilitates sedation with propofol for routine ERCP: a randomized, controlled trial. Gastrointest Endosc. 2002;56:817–24.
12. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, et al. Validity and reliability of the Observer's assessment of alertness/sedation scale: study with intravenous midazolam. J Clin Psychopharmacol. 1990;10:244–51.
13. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
14. Ki S, Lee D, Lee W, Cho K, Han Y, Lee J. Verification of the performance of the bispectral index as a hypnotic depth indicator during dexmedetomidine sedation. Anesth Pain Med (Seoul). 2022;17:44–51.
15. Gélinas C, Tousignant-Laflamme Y, Tanguay A, Bourgault P. Exploring the validity of the bispectral index, the critical-care pain observation tool and vital signs for the detection of pain in sedated and mechanically ventilated critically ill adults: a pilot study. Intensive Crit Care Nurs. 2011;27:46–52.
16. Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology. 2000;93: 1336–44.
17. Andrzejowski J, Sleigh JW, Johnson IA, Sikiotis L. The effect of intravenous epinephrine on the bispectral index and sedation. Anaesthesia. 2000;55:761–3.
18. Faritous Z, Barzanji A, Azarfarin R, Ghadrdoost B, Ziyaeifard M, Aghdaei N, et al. Comparison of bispectral index monitoring with the critical-care pain observation tool in the pain assessment of intubated adult patients after cardiac surgery. Anesth Pain Med. 2016;6:e38334.

How to cite this article: Yamada J, Hazama D, Tachihara M, Kawanami Y, Kawaguchi A, Yatani A, et al. The utility of bispectral index monitoring in flexible bronchoscopy: A single-center, retrospective observational study. Thorac Cancer. 2022;13(21): 3052–7. https://doi.org/10.1111/1759-7714.14658