

Age-dependent relationship between bispectral index and the sedation level

Running title: Age on sedation and BIS

Kazunori Yamashita M.D. (1), Yoshiaki Terao M.D. (1), Chiaki Inadomi M.D. (2), Masafumi Takada M.D. (2), Makoto Fukusaki M.D. (1), Koji Sumikawa M.D. (2)

(1) Department of Anesthesia, Nagasaki Rosai Hospital

2-12-5 Setogoshi, Sasebo 857-0134, Japan

(2) Division of Anesthesiology Department of Translational Medical Science, Nagasaki

University School of Medicine

1-7-1 Sakamoto, Nagasaki 857-8501, Japan

The present address of Kazunori Yamashita, Chiaki Inadomi and Masafumi Takada is Division of Anesthesiology Department of Translational Medical Science, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 857-8501, Japan.

Address correspondence and reprint request to Kazunori Yamashita MD

Division of Anesthesiology Department of Translational Medical Science, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 857-8501, Japan. Telephone number: +81-95-819-7370; Fax number: +81-95-819-7373; E-mail: kazy@plum.ocn.ne.jp

(Abstract)

**Study Objective:** To determine the relationship between bispectral index ( BIS) and the sedation

**Design:** Prospective, observational clinical study

**Setting:** Intensive care unit of public hospital in Japan

**Patients:** 22 patients undergoing postoperative sedation with midazolam

**Interventions:** The patients were allocated into 2 groups, group M (middle aged, <65 years) and group H (elderly, >65 years). Midazolam was administered at a bolus dose of  $0.1 \text{ mg} \cdot \text{kg}^{-1}$ , followed by a continuous dose of  $0.04 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ , which was adjusted every 2 hrs to achieve a target level of sedation at 3-6 on Ramsay sedation scale (RSS), and buprenorphine was administered at a constant rate ( $0.625 \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ ).

**Measurements:** BIS value, RSS, the dose of midazolam, body temperature, heart rate, the dose of dopamine, and mean arterial pressure were recorded every 2 hrs by an independent nurse. Data were analyzed using Spearman's rank correlation and Mann-Whitney U test.

**Main Results:** The BIS values decreased depending on the depth of sedation, and there were significant correlation between RSS and BIS in both groups. The BIS values at levels of RSS 5 and 6 were significantly lower in group H than in group M.

**Conclusion:** BIS correlated with sedation depth, and BIS in older patients were lower than that in middle-aged patients at a deep sedation depth.

**Key words:** bispectral index, age, sedation level

## Introduction

During continuous sedation in the intensive care unit (ICU), the evaluation of the depth of sedation is important to facilitate the titration of sedatives, as well as to prevent excessive sedation<sup>1,2</sup>. Ramsay sedation scale (RSS; Table 1) and Sedation-agitation scale are widely used as subjective evaluations of the depth of sedation, and the usefulness of these assessment methods are proved<sup>3,4</sup>.

Although the subjective method to evaluate the depth of sedation has been established, an objective method has not been established. Auditory evoked potential and oxygen consumption index ( $\dot{V}O_2I$ ) are the procedures for the objective evaluation of the depth of sedation<sup>3,5</sup>. The bispectral index (BIS), has been used to evaluate the anesthetic depth, and the usefulness in the operating room has been established<sup>6-10</sup>. The usefulness of BIS in ICU to evaluate sedation depth is controversial. The main reason not to recommend the use of BIS in ICU is some interference of electromyogram (EMG) including shivering<sup>11,12</sup>. On the other hand, Schultz et al.<sup>13</sup> reported that the hypnotic effect of propofol and the spectral patterns in the EEG in elderly patients were different from those in younger patients.

The present study was carried out to determine whether the relationship between BIS and the level of sedation produced by midazolam might be influenced by age. We compared BIS under the same sedation level between elder and middle-aged patients.

## Materials and Methods

### Patients

This study was approved by the Institutional Ethics Committee, and written informed consent was obtained from each patient. We studied 22 consecutive patients (15 men and 7 women) who required mechanical ventilation overnight postoperatively in the ICU. The patients were allocated into one of two groups, i.e., group M (middle-aged patients, age 20 - 65; n=8) and group H (high-aged patients, age > 65 years; n=14). This study's inclusion criteria were as follows: a) elective abdominal major surgery (operation time > 4 hr); b) ASA physical status 1-3; and c) ages over 19 years old. Patients with central nervous or cerebrovascular diseases, patients with alcoholism or patients taking anxiolytics/hypnotics were excluded.

### Therapy

All patients received conventional intensive care therapy according to clinical requirements. The physicians adjusted dopamine to maintain an adequate mean arterial blood pressure, and the ventilator setting to maintain clinically appropriate gas exchange. Patients' lungs were ventilated with synchronous intermittent mandatory ventilation mode or continuous positive airway pressure mode. Continuous hemodynamic monitoring consisted of electrocardiogram, heart rate, and direct arterial blood pressure.

### Sedation

All patients received analgesia with a continuous infusion of buprenorphine at a fixed dose of  $0.625 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ . Patients did not receive other analgesics or nonsteroidal

anti-inflammatory drugs. Midazolam was used for maintenance of intravenous sedation after admission to the ICU. After the bolus dose of midazolam ( $0.1 \text{ mg} \cdot \text{kg}^{-1}$ ), the continuous dose was started at  $0.04 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ , and adjusted every 2 hrs to achieve a target level of sedation at the scores of 3-6 on RSS. The dose of midazolam was adjusted by varying the dose by 10 %-increase or decrease to maintain the adequate depth of sedation. If necessary, additional bolus of midazolam ( $0.1 \text{ mg} \cdot \text{kg}^{-1}$ ) was administered intravenously. The dosage was not changed for 1 hr before the measurement, and bolus dose of midazolam was not administered for 1 hr before the measurement.

#### Study Procedure

The BIS sensor (A2000 BIS monitoring system, Aspect Medical System, Natick, MA, USA) was applied to each patient. The bedside nurse was blinded to the BIS value. After the body temperature returned to greater than  $36^\circ \text{C}$ , BIS value was recorded every 2 hrs by an independent nurse. Mean arterial blood pressure (MAP), heart rate (HR), body temperature (BT) and RSS were recorded by another nurse blinded to BIS, immediately after the BIS measurement.

#### Statistical Analysis

The results were expressed as mean  $\pm$  SD. Statistical analysis of the differences between the two groups was performed using Mann-Whitney U test. Spearman's correlation was used to examine possible relationship between RSS and the other parameters including BIS.  $P < 0.05$  was considered significant.

## Results

A total of 115 measurements were recorded in 22 patients: 41 measurements of 8 middle-aged patients, 74 measurements of 14 elderly patients. No patient was excluded after enrollment into the study.

There were significant differences in the mean height and weight between group M and group H, and there was no significant difference in the duration of sedation between two groups. There was no difference in the total dose of midazolam between group M and group H (Table 2).

The operation procedures were total gastrectomy (6 cases), pancreatoduodenectomy (5), rectal amputation (4), hepatectomy (4), low anterior colon resection (2), and cystectomy with ureteroileostomy (1).

Table 3 shows the BIS values, vital signs and the dose of drugs in both groups. BIS had the significant differences in RSS 5 and 6, HR in RSS 5, and MAP in RSS 3.

Figure 1 shows the relationships between RSS and BIS in both groups. There are significant correlations between RSS and BIS in both groups. At heavy sedation (RSS 5 or 6), BIS in group H is significantly lower than that in group M ( $p < 0.05$  with Mann-Whitney U test).

## Discussion

The present results show that there are significant correlation between RSS and BIS in group M and group H, and at heavy sedation (RSS 5 or 6), BIS in group H is significantly lower than that in group M ( $p < 0.05$  with Mann-Whitney U test).

In the present study, the patients received continuous infusion of midazolam, and the dosage varied to achieve a desired RSS. Although the BIS value declined as the sedation depth became heavier in both groups, the BIS value at heavier sedation showed different values between group M and group H. Reasons for the age-related difference of BIS are not yet clear.

First, there might be a bias of BIS monitor. BIS is used for the evaluation of the depth of anesthesia. The usefulness of BIS is controversial<sup>1, 11, 12, 14</sup> for evaluating the depth of sedation in ICU. Nasraway et al.<sup>11</sup> suggested that regular/ routine use of BIS should not be used to monitor critically ill patients receiving no neuromuscular blockade. They reported that the EMG activity interference was one of the most important limitations and pitfalls to BIS monitoring in ICU patients<sup>11</sup>. In the present study, neuromuscular blockade was reversed in the operating room, and most patients shivered immediately after transfer to ICU due to mild hypothermia. Thus, we did not start the measurements until BT rose back to 36 ° C. We did not monitor EMG activities, but all BIS measurements were done with signal quality index (SQI) of BIS over 50 referred to Johansen's report<sup>15</sup>. EMG activity may have an influence on the present study, even though we did not observe shivering during the measurements, some kind of EMG activities might influence on the present study.

Second, there may be an age-specific EEG response to sedatives. Schultz et al. showed that age-related changes in the spectral parameters of the EEG signal before and during induction of propofol anesthesia<sup>13</sup>. The age-related effects of midazolam on the spectral parameters of EEG is not clear, which might influence BIS at heavy sedation in elderly.

Third, the effect of midazolam might influence the age-dependent relationship. It is known that the ED<sub>50</sub> of midazolam is lower in the elderly, while the doses of midazolam were similar between the two groups in the present study. Thus the effect of midazolam might have caused heavier sedation in the elderly.

When a patient is under heavy sedation, the blood pressure tends to decrease. In the present study, we adjusted the dose of dopamine to maintain adequate mean arterial pressure. Although the dopamine dosages tended to be greater in the heavily sedated patients, there was no difference in the dosages between two groups. Thus the blood pressure would not have influenced the age-dependent relationship.

Concerning the effect of body temperature (BT), Mathew et al reported that BIS is estimated to decrease by 1.12 units for each degree Celsius decrease in hypothermic state<sup>14</sup>. On the other hand, some authors reported the significant correlation between BIS and BT<sup>16,17</sup> in non-hypothermic state. In this study, no patients were in hypothermic state, thus the age-dependent BIS change might be relevant to the BT change.

In conclusion, when BIS is applied to sedated patients in the ICU, BIS changes in accordance with sedation depths. There is an age-dependency in the relationship between BIS and sedation

level, i.e., BIS is lower in high-aged patients than in middle-aged patients when compared at a deep sedation level.

Acknowledgement: This research was supported by research funds to promote the hospital functions of Japan Labor Health and Welfare Organization.

**Table 1. Ramsay sedation scale**

<b>Score</b>	<b>Description</b>	<b>Definition</b>
<b>1</b>	<b>Awake</b>	<b>Anxious and agitated</b>
<b>2</b>	<b>Awake</b>	<b>Cooperative, tranquil, oriented</b>
<b>3</b>	<b>Awake</b>	<b>Responds only to verbal command</b>
<b>4</b>	<b>Asleep</b>	<b>Asleep with brisk response to light stimulation</b>
<b>5</b>	<b>Asleep</b>	<b>Asleep without response to light stimulation</b>
<b>6</b>	<b>Asleep</b>	<b>Non responsive</b>

**Table 2. Backgrounds**

	<b>M (8)</b>	<b>H (14)</b>
<b>Age (y.o.)</b>	<b>54 ± 4</b>	<b>77 ± 4 #</b>
<b>Sex (M/F)</b>	<b>6/2</b>	<b>9/5</b>
<b>Height (cm)</b>	<b>164 ± 6</b>	<b>155 ± 8 #</b>
<b>Weight (kg)</b>	<b>62 ± 11</b>	<b>56 ± 11 #</b>
<b>Duration (min)</b>	<b>809 ± 158</b>	<b>830 ± 85</b>
<b>Total Mz (mg·kg<sup>-1</sup>)</b>	<b>1.09 ± 0.50</b>	<b>0.83 ± 0.26</b>

**NOTE.** Values are mean ± SD, Statistics. Mann-Whitney U test

**Abbreviations:** M, middle-aged patients < 65 years old;

**H, high-aged patients ≥ 65 years old; Duration, duration of sedation; Total Mz, total dose of midazolam**

**# p < 0.05 vs. middle-aged patients**

**Table 3. BIS, vital signs and doses of drugs**

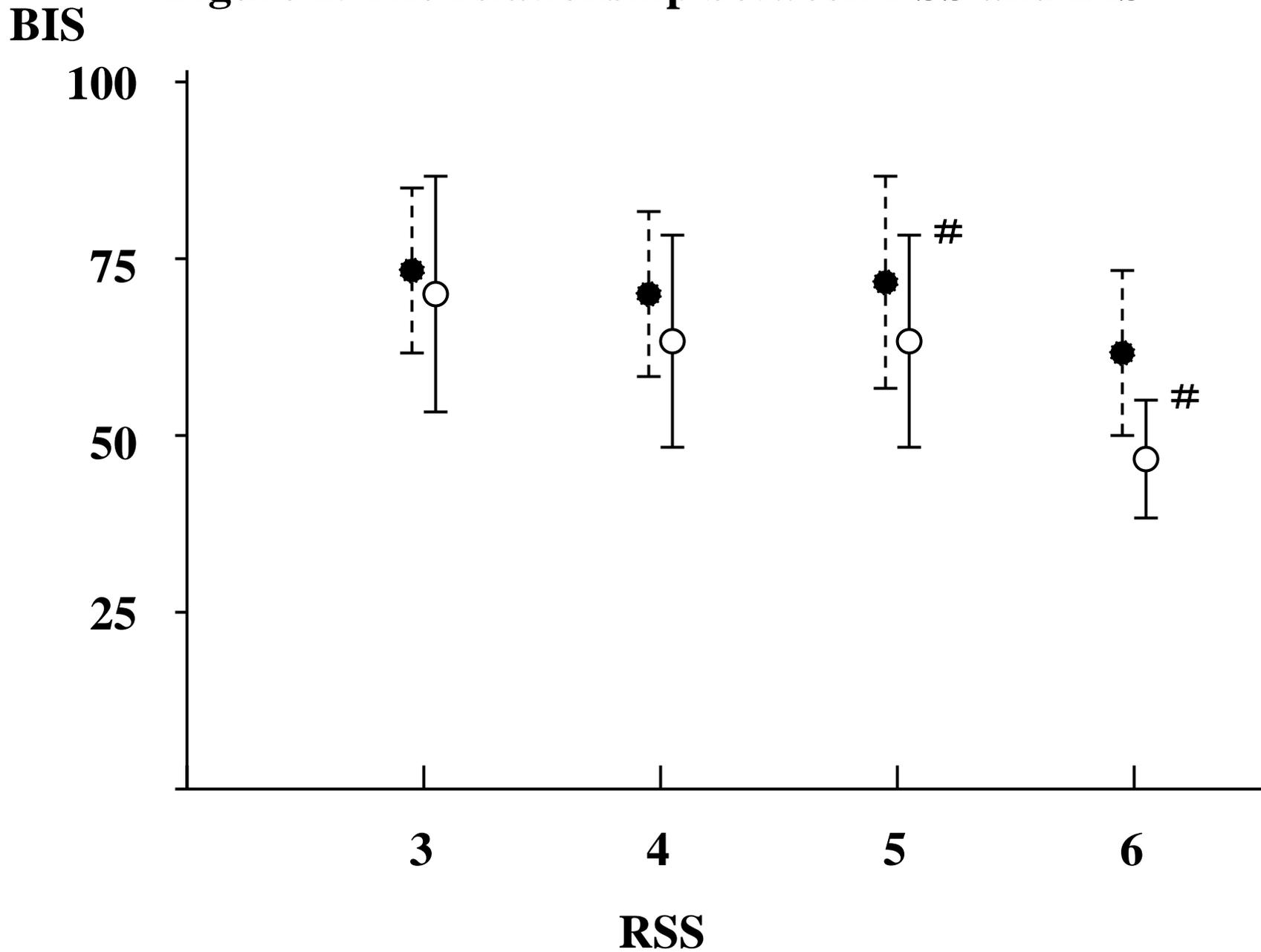
Parameters	Groups	Values			
		3	4	5	6
BIS	M	74±9 (n=15)	70±10 (n=8)	72±12 (n=10)	62±10 (n=8)
	H	70±15 (n=20)	67±13 (n=16)	64±13 # (n=25)	46±7 # (n=13)
HR (bpm)	M	88±18	82±14	97±14	88±16
	H	82±16	82±12	74±17 #	87±11
DOA ( $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ )	M	0	1.1±2.1	1.1±2.4	0
	H	1.4±3.5	0.9±2.5	3.8±4.3	2.4±3.7
MAP (mmHg)	M	89±9	90±12	84±8	84±14
	H	81±13 #	88±13	84±19	86±16

**NOTE.** Values are mean  $\pm$  SD, Statistics. Mann-Whitney U test

**Abbreviations:** HR, heart rate; DOA, the dose of dopamine; MAP, mean arterial pressure; M, middle-aged patients; H, high-aged patients; n, number of patients

# p<0.05, v.s.middle-aged patients

**Figure 1. The relationship between RSS and BIS**



## References

1. Jacobi J, Fraser GL, Coursin DB, et al.:

Clinical practice guidelines for the sustained use of sedatives and analgesia in the critically ill adult.

Crit Care Med 2002; 30: 119- 41, 2002

2. Young C, Knudsen N, Hilton A, Reves JG:

Sedation in the intensive care unit.

Crit Care Med 2000; 28: 854-66,

3. Schulte-Tamburen AM, Scheier J, Briegel J, Schwender D, Peter K:

Comparison of five sedation scoring systems by means of auditory evoked potentials.

Intensive Care Med 1999; 25: 377- 82

4. Devlin JW, Fraser GL, Kanji S, Riker RR:

Sedation assessment in critically ill adults.

Ann Pharmacother 2001; 35: 1624- 32

5. Terao Y, Miura K, Saito M, Sekino M, Fukusaki M, Sumikawa K:

Quantitative analysis of the relationship between sedation and resting energy expenditure in postoperative patients.

Crit Care Med 2003; 31: 830- 3

6. Gan TJ, Glass PS, Windsor A, et al.:

Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and

nitrous oxide anesthesia.

Anesthesiology 1997; 87: 808- 15

7. 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

8. Lehmann A, Karzau J, Boldt J, Thaler E, Lang J, Isgro F:

Bispectral index-guided anesthesia in patients undergoing aortocoronary bypass grafting.

Anesth Analg 2003; 96: 336- 43

9. Song D, Joshi GP, White PF:

Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia.

Anesthesiology 1997; 87: 842- 8

10. Forestier F, Hirschi M, Rouget P, et al.:

Propofol and sufentanil titration with the bispectral index to provide anesthesia for coronary artery surgery.

Anesthesiology 2003; 99: 334- 46

11. Nasraway SA SA Jr, Wu EC, Kelleher RM, Yasuda CM, Donnelly AM:

How reliable is the Bispectral Index in critically ill patients? A prospective, comparative, single-blinded observer study.

Crit Care Med 2002; 30: 1483- 7

12. Vivien B, Di Maria S, Ouattara A, Langeron O, Coriat P, Riou B:

Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant.

Anesthesiology 2003, 99: 9-17

13. Schultz A, Grouven U, Zander I, Beger FA, Siedenberg M, Schultz B:

Age-related effects in the EEG during propofol anaesthesia.

Acta Anaesthesiol Scand 2004;48: 27-34

14. Mathew JP, Weatherwax KJ, East CJ, White WD, Reves JG:

Bispectral analysis during cardiopulmonary bypass: The effect of hypothermia on the hypnotic state

J Clin Anesth 2001; 13; 301-5

15. Johansen JW:

Logistic of 24 hour bispectral index monitoring in the ICU

Anesth Analg 2000; 90; S212

16. RiessML, Graefe UA, Goeters C, Van Aken H, Bone HG

Sedation assessment in critically ill patients with bispectral index

Eur J Anaesthesiol 2002; 19; 18-22

17. Tonner PH, Weil C, Bein B, Weiler N, Paris A, Scholz J

Comparison of two bispectral index algorithms in monitoring sedation in postoperative intensive care patients

Crit Care Med 2005; 33; 580-584