ORIGINAL ARTICLE

Gut and Liver, Vol. 5, No. 2, June 2011, pp. 160-164

Efficacy of Bispectral Index Monitoring for Midazolam and Meperidine Induced Sedation during Endoscopic Submucosal Dissection: A Prospective, Randomized Controlled Study

Ki Joo Kang, Byung-Hoon Min, Mi Jung Lee, Hyun Sook Lim, Jin Yong Kim, Jun Haeng Lee, Dong Kyung Chang, Young-Ho Kim, Poong-Lyul Rhee, Jong Chul Rhee, and Jae J. Kim

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background/Aims: Propofol induced sedation with bispectral index (BIS) monitoring has been reported to lead to higher satisfaction in patients and endoscopists during endoscopic submucosal dissection (ESD) procedures. There are no data, however, regarding the efficacy of midazolam and meperidine (M/M) induced sedation with BIS monitoring during ESD. The purpose of this study was to evaluate whether M/M induced sedation with BIS monitoring could improve satisfaction and reduce the dose of M/M required during ESD. **Methods:** Between September 2009 and January 2010, 56 patients were prospectively enrolled and randomly assigned to a BIS group (n=28) and a non-BIS group (n=28). Patient and endoscopist satisfaction scores were assessed using the visual analog scale (0 to 100) following the ESD. **Results:** The mean satisfaction scores did not significantly differ between the BIS and non-BIS groups (92.3±16.3 vs 93.3±15.5, p=0.53) or endoscopists (83.1±15.4 vs 80.0±16.7, p=0.52). Although the mean meperidine dose did not differ (62.5±27.6 vs 51.0±17.3, p=0.18) between the two groups, the mean dose of midazolam in the non-BIS group was lower than in the BIS group (6.8±2.0 vs 5.4±2.1, p=0.01). **Conclusions:** BIS monitoring during ESD did not increase the satisfaction of endoscopists or patients and did not lead to an M/M dose reduction. These results demonstrate that BIS monitoring provides no additional benefit to M/M induced sedation during ESD. **(Gut Liver 2011;5:160-164)**

Key Words: Bispectral index monitoring; Satisfaction; Midazolam; Endoscopic submucosal dissection

INTRODUCTION

Recently, endoscopic submucosal dissection (ESD) has been widely used for the resection of early gastric cancers and gastric adenomas. ESD is useful for complete histological evaluation of the tumor as well as curative resections because of the en bloc resection.[1] Although ESD is less invasive and safer method than surgery,[2-4] it is a technically difficult procedure; it has a higher incidence of complications and requires a longer operation time than conventional endoscopic mucosal resection (EMR). Therefore, ESD must require the appropriate sedation of patients without increasing complications.

The bispectral index (BIS) value is based on a calibrated number on the electroencephalograph of the frontal cortex corresponding to varying levels of sedation, ranging from 0 to 100 (0, no cortical activity or coma; 40 to 60, unconscious; 70 to 90, varying levels of conscious sedation; 100, fully awake).[5,6]

BIS monitoring has been used to minimize complications that may occur during sedation and to evaluate by objective measures the level of sedation instead of using the conventional measures such as Modified Observer's Assessment of Alertness and Sedation (MOAA/S).[7-9] There were temporal correlations between BIS levels and MOAA/S scores in previous studies.[6,10,11]

Although several studies showed no clinical role of BIS monitoring during endoscopic sedation,[12,13] BIS monitoring during ESD procedures with the propofol induced sedation lead to higher satisfaction scores among patients and endoscopists.[14] Propofol has several advantages with regard to maintaining deep sedation and reducing patient anxiety, as well as pain and discomfort during the procedure.[15,16] Recently, the number of gastroenterologists administering propofol directly for endo-

Correspondence to: Jae J. Kim
Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3409, Fax: +82-2-3410-6983, E-mail: jjkim@skku.edu
Received on October 11, 2010. Accepted on November 10, 2010.
pISSN 1976-2283 eISSN 2005-1212 DOI: 10.5009/gnl.2011.5.2.160

scopic sedation is increasing, and several studies showed the safety of administering propofol by endoscopist.[17,18] However, the indications of propofol for sedation in various countries still imply that it should be used only by anesthesiologists or by intensive-care specialists owing to the narrow therapeutic effect of propofol.[19] Instead of propofol, other sedative drugs such as midazolam and meperidine are safe and useful for diagnostic and therapeutic endoscopy without assist of anesthetics or intensive-care specialists for supervision. Midazolam with meperidine is more frequently used wherever anesthesiologists are not available. However, midazolam with meperidine have a longer half-life than propofol and long procedure during ESD could be at high risk of accumulation of the drugs. Therefore, we performed a randomized prospective study to evaluate whether BIS monitoring during sedation induced by midazolam and meperidine could improve the satisfaction of the endoscopists and patients and reduce the dose of drugs. We also evaluated the efficacy of the BIS monitor in preventing adverse effects of sedation during ESD procedure.

MATERIALS AND METHODS

1. Patients

From September 2009 and January 2010, we prospectively enrolled 56 patients who were randomized to BIS group (n=28) or non-BIS group (n=28). ESD was performed for gastric adenomas, differentiated-type gastric cancers greater than 30 mm in diameter without ulceration and gastric cancers up to 30 mm with ulceration, or minute submucosal invasion. Patients were excluded if they were under 18 years of age, had an ASA classification of 4 to 5, were pregnant, had a history of stroke or an allergy to sedative drugs. This protocol was approved by the Institutional Review Board at Samsung Medical Center.

The sample size was calculated as the difference in the satisfaction score (0 to 10) of more than two points between the BIS group and non-BIS group. Assuming a standard deviation of patients satisfaction between the BIS group and non-BIS group as 1.87 and 3.03, respectively, each group required 28 patients (α =0.05, power=80%). Sixty lesions in 56 patients were included. All of the study patients were randomly divided into one of two groups by the SPSS program (SPSS Inc., Chicago, IL, USA). The level of sedation in the BIS group was monitored using BIS, and the level of sedation in non-BIS group was monitored using MOAA/S.

The ESD procedure was performed by one experienced therapeutic endoscopist (Jae J. Kim). Blood pressure, heart rate, oxygen saturation, and the depth of sedation were checked using standard monitoring systems during procedure. All parameters were recorded every three minutes and the time of all events was recorded in two groups. The patients and endoscopist could not watch the BIS monitoring during the procedure. The assistant could not see the BIS score during ESD procedure in non-BIS group. The score for satisfaction was obtained from both the patients and endoscopist after the ESD and the scores for recall of pain during the procedure were recorded. The scores ranged from 0 to100 (the lowest score, 0, the highest score, 100), using the 100 mm visual analog scale.

2. Monitoring of alertness and sedation

MOAA/S scores range from 1 to 5: unresponsive to shaking, 1; responsive to shaking only, 2; responsive to normal verbal commands, 3; lethargic but responsive to normal verbal commands, 4; responsive and alert, 5.[20] The level of sedation with BIS scores was defined as follows: >85 (awake), 76 to 85 (moderate sedation), 66 to 75 (deep sedation), and 45 to 65 (general anesthesia). The target level of sedation in this study was moderate to deep sedation for the ESD. This level was achieved with a score of 2 or 3 on the MOAA/S and that for the BIS was 65 to 80.

3. Sedative dosage

The initial intravenous dose of midazolam was 0.03 mg/kg in patients less than 60 years of age and 60 kg, 2 mg in patients less than 60 years of age and more than 60 kg, and 1 mg in patients more than 60 years old. The initial intravenous dose of meperidine was 25 mg in patients less than 60 kg, and 50 mg in patients less than 60 years old and more than 60 kg. If additional doses were needed (MOAA/S score $\geq$4 or BIS score >80), midazolam (0.5 to 1 mg) or meperidine (25 mg) was added.

4. Statistical methods

Baseline data from the patients in the two groups were compared by chi-square test or Fisher's exact test for categorical variables. A Student's t-test for normally distributed continuous variables and a Mann-Whitney test for non-normally distributed continuous variables were used. For the analysis of a correlation between the BIS and MOAA scores, the correlation coefficient with repeated observations reported by Bland and Altman was used in non-BIS group. Before the analysis, the BIS was log-transformed to approximate a normal distribution.

RESULTS

1. Patient characteristics

Fifty-six patients were enrolled and 6 patients (2 patients in BIS group and 4 patients in non-BIS group) were dropped from the study because of paradoxical reactions during the procedure. There was no statistical difference in baseline characteristics of the patients between the two groups (Table 1). Although the tumor size of the lesions in non-BIS group was smaller than in BIS group (p=0.03), there was no statistical difference in the resected tumor size, procedure time, and curative resection rates between the two groups (Table 2).

Table 1. Baseline Characteristics of Patients in the BIS and Non-BIS Groups

	BIS group (n=26)	Non-BIS group (n=24)	p-value
Mean age	60.8±10.0	58.3±9.6	0.384
Male:Female	19:7	20:4	0.501
Mean BMI, kg/m^2	23.7±2.7	24.4±2.9	0.696
Concurrent narcotic or anxiolytic medication use	6 (23)	2 (8.3)	0.250
Alcohol	12 (46.2)	5 (20.8)	0.078
Smoking	6 (23)	7 (29.2)	0.623
ASA classification			0.679
1	17 (65.4)	17 (79.8)	
2	9 (34.6)	7 (29.2)	

Data are presented as mean±SD or number (%).
BIS, bispectral index monitoring; BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2. Endoscopic and Pathological Characteristics of the Two Groups

	BIS group	Non-BIS group	p-value
No. of lesions	29	25	
Tumors			0.123
Adenoma	7 (24.1)	11 (44)	
Cancer	22 (75.9)	14 (56.0)	
Location			0.838
Lower	18 (62.1)	14 (56)	
Middle	8 (27.6)	9 (36)	
Upper	3 (10.3)	2 (8)	
Resected tumor size, mm	40.3±13.6	40.9±16.1	0.875
Size of lesion, mm	17.6±11.9	11.6±7.6	0.03
Procedure time, min	58.1±29.2	47.0±23.5	0.128
Curative resection	26 (89.7)	22 (88)	NS

Data are presented as mean±SD or number (%).
BIS, bispectral index monitoring; NS, not significant.

2. Dose of sedative drug and satisfaction score

The dose of midazolam used in the BIS group was larger than in non-BIS group (p=0.01). The mean dose of midazolam and meperidine used in BIS group was 6.8±2.0 mg and 62.5±27.6 mg, respectively. That used in non-BIS group was 5.4±2.1 mg and 51.0±17.3 mg, respectively.

There was no significant difference between the two groups with regard to recall of pain during the procedure and satisfaction with sedation (Table 3). Table 4 showed hemodynamic parameters, BIS monitoring, and complications. There was no blood pressure drop below 90 mmHg during the sedation. The mean BIS score in BIS group was lower than in non-BIS group (p<0.01). Hypoxemia (SpO_2 <90%) was detected in both groups (8 patients in BIS group and 6 patients in non-BIS group), which recovered soon after oxygen was provided. The delayed bleeding and perforation rate did not showed significant difference in two scoring system.

Table 3. Sedative Drug Doses and Satisfaction Scores of the Two Groups

	BIS group (n=26)	Non-BIS group (n=24)	p-value
Sedation drug			
Mean dose of midazolam, mg	6.8±2.0	5.4±2.1	0.01
Mean dose of meperidine, mg	62.5±27.6	51.0±17.3	0.18
Satisfaction score			
Recall of procedure	13.5±28.0	22.5±35.7	0.47
Pain	12.7±27.4	15.8±30.4	0.97
Patients	92.3±16.3	93.3±15.5	0.53
Endoscopist	83.1±15.4	80.0±16.7	0.52

Data are presented as mean±SD.
Recall scores, pain scores, and satisfaction scores range from 0 to 100 (lowest score, 0; highest score, 100).
BIS, bispectral index monitoring.

Table 4. Hemodynamic, BIS, and Complications

	BIS group (n=26)	Non-BIS group (n=24)	p-value
Mean BP, mm Hg	120.9±16.16	119.21±13.46	0.693
Mean heart rate	69.27±14.21	70.46±12.64	0.756
Mean BIS	77.0±2.69	80.3±4.84	<0.01
SpO_2 <90%	8 (30.1)	6 (25)	0.649
Electrocautery	1 (3.8)	1 (4.2)	NS
Perforation	1 (3.8)	0	NS

Data are presented as mean±SD or number (%).
Mean BP=(2*systolic BP+ diastolic BP)/3.
BIS, bispectral index monitoring; BP, blood pressure; NS, not significant.

We additionally investigated that the correlation of BIS levels and MOAA/S scores during ESD procedure because there was no data of correlation between two scoring systems in ESD procedure. The mean scores of BIS and MOAA/S was 80.1±5.9 (range, 66 to 98) and 2.8±0.7 (range, 1 to 4), respectively. Two scoring systems showed weak correlation in ESD procedure with midazolam and meperidine induced sedation (correlation coefficient=0.274, p<0.001).

DISCUSSION

Several sedative drugs and a variety of combinations such as propofol with or without a benzodiazepine or opioid, benzodiazepine plus an opioid, a benzodiazepine alone, entonox, and others, are used for sedation during endoscopic procedures.[21]

Propofol has a very rapid onset of action and a short half life; it is associated with a fast recovery time from the sedation. Several studies have shown that propofol was superior to benzodiazepines and narcotics with regard to rapid induction of sedation and fast recovery.[22-25] A recent study showed a higher satisfaction with BIS monitoring of propofol induced sedation during ESD procedures.[14] However, propofol has a narrow therapeutic range and older patients have an increased sensitivity to its effects. In addition, it has no analgesic effects and narcotics are required during painful procedures. The combined use of narcotics or benzodiazepines can add to the risk of respiratory depression caused by unplanned deep sedation and general anesthesia. Although propofol induced sedation was safe with appropriate monitoring systems, the nurse or endoscopist administrated propofol induced sedation is not yet generally recommended in various countries.

The combination of midazolam and meperidine for sedation without assistance of anesthetics or intensive-care specialists is safe and useful. Therefore, we investigated whether midazolam and meperidine induced sedation using BIS monitoring affect the satisfaction of patients and endoscopist in lengthy and complicated ESD procedure. Contrary to our expectations, the overall satisfaction of the patients and endoscopist, the complication rate, and the patients' recall of pain during the ESD procedure, did not differ in the comparisons between BIS and non-BIS groups. In addition, subgroup analysis of ESD procedure taking more than 60 minutes did not showed statistical difference of satisfaction of patients and endoscopist. This findings suggest that BIS monitoring system for midazolam and meperidine induced sedation during ESD procedure do not give the additional efficacy of increasing satisfaction and decreasing complication rate. This was consistent with other studies which demonstrated that BIS monitoring did not improve any measure of patients outcome during endoscopic sedation.[12,13] The midazolam and meperidine being used for sedation require 2 to 6 minutes for peak effect. Consequently, an under-sedated patient with a BIS level of 88 will remain under-sedated. Therefore, the value of BIS as an "early warning" sign of patient under sedation is not fully appreciated with midazolam and meperidine induced sedation.

We excluded 2 patients in BIS group and 4 patients in non-BIS group because of paradoxical reaction. Generally, the incidence rate of paradoxical reaction was reported less than 1 percent during midazolam induced sedation.[26] However, other study reported that a lengthy and painful procedure such as ERCP was more frequently experienced paradoxical reaction because of increased anxiety before performing procedure.[25] The high incidence of paradoxical reaction in this study may be associated with anxiety of patients due to invasive ESD procedure.

Several reports showed temporally significant correlation BIS levels and MOAA/S scores.[6,11,27,28] However, there was weak correlation between BIS levels and MOAA/S scores in this study. This finding might be induced from the feature of lengthy and invasive ESD procedure of our study compared to previous reports which included in the simple diagnostic and short duration of endoscopic procedures.

In this study, the mean dose of midazolam in non-BIS group was lower than in the BIS group. This finding might be explained by the following. First, there was a significant overlap of the BIS scores between the deep and moderate levels of sedation. Second, the BIS scores were generally more specific than sensitive for the levels of deep sedation, i.e., more sedative drugs might be administrated to patients with BIS monitoring even with adequate sedation.[11]

Although midazolam and meperidine induced sedation using BIS monitoring did not showed efficacy, this was the first study to evaluate the usefulness of BIS monitoring with midazolam and meperidine induced sedation during ESD procedures.

In conclusion, the results of this study show that midazolam and meperidine induced sedation using BIS monitoring do not provide to increase satisfaction of patients and endoscopist, to decrease complication rate, and to reduce dose of midazolam and meperidine during ESD procedures. Thus, we suggest that BIS monitoring does not have additional role in the the midazolam and meperidine induced sedation during ESD procedure.

ACKNOWLEDGEMENTS

Conflict of interest statement: All of doctors have no conflicts of interest or financial ties to disclose. They agreed to sign the Copyright Transfer Statement. This manuscript was written entirely by the authors, with no external assistance. No grant support was received for this study.

REFERENCES

1. Imagawa A, Okada H, Kawahara Y, et al. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. Endoscopy 2006;38:987-990.
2. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-229.
3. Ohkuwa M, Hosokawa K, Boku N, Ohtu A, Tajiri H, Yoshida S. New endoscopic treatment for intramucosal gastric tumors using an insulated-tip diathermic knife. Endoscopy 2001;33:221-226.
4. Yahagi N, Fujishiro M, Kakushima N, et al. Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). Dig Endosc 2004;16:34-38.
5. Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology 2000;93:1336-1344.
6. Bower AL, Ripepi A, Dilger J, Boparai N, Brody FJ, Ponsky JL. Bispectral index monitoring of sedation during endoscopy. Gastrointest Endosc 2000;52:192-196.
7. Struys M, Versichelen L, Byttebier G, Mortier E, Moerman A, Rolly

G. Clinical usefulness of the bispectral index for titrating propofol target effect-site concentration. Anaesthesia 1998;53:4-12.
8. Rosow C, Manberg PJ. Bispectral index monitoring. Anesthesiol Clin North America 2001;19:947-966, xi.
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;86:836-847.
10. Chen SC, Rex DK. An initial investigation of bispectral monitoring as an adjunct to nurse-administered propofol sedation for colonoscopy. Am J Gastroenterol 2004;99:1081-1086.
11. Qadeer MA, Vargo JJ, Patel S, et al. Bispectral index monitoring of conscious sedation with the combination of meperidine and midazolam during endoscopy. Clin Gastroenterol Hepatol 2008;6:102-108.
12. Drake LM, Chen SC, Rex DK. Efficacy of bispectral monitoring as an adjunct to nurse-administered propofol sedation for colonoscopy: a randomized controlled trial. Am J Gastroenterol 2006;101:2003-2007.
13. DeWitt JM. Bispectral index monitoring for nurse-administered propofol sedation during upper endoscopic ultrasound: a prospective, randomized controlled trial. Dig Dis Sci 2008;53:2739-2745.
14. Imagawa A, Fujiki S, Kawahara Y, et al. Satisfaction with bispectral index monitoring of propofol-mediated sedation during endoscopic submucosal dissection: a prospective, randomized study. Endoscopy 2008;40:905-909.
15. American Society of Anesthesiologists Task Force on Sedation and Analgesia by Non-Anesthesiologists. Practice guidelines for sedation and analgesia by non-anesthesiologists. Anesthesiology 2002;96:1004-1017.
16. Faigel DO, Baron TH, Goldstein JL, et al. Guidelines for the use of deep sedation and anesthesia for GI endoscopy. Gastrointest Endosc 2002;56:613-617.
17. Bell GD. Preparation, premedication, and surveillance. Endoscopy 2004;36:23-31.
18. Lazzaroni M, Bianchi Porro G. Preparation, premedication and surveillance. Endoscopy 2003;35:103-111.
19. Waring JP, Baron TH, Hirota WK, et al. Guidelines for conscious sedation and monitoring during gastrointestinal endoscopy. Gastrointest Endosc 2003;58:317-322.
20. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: study with intravenous midazolam. J Clin Psychopharmacol 1990;10:244-251.
21. Bell GD. Premedication, preparation, and surveillance. Endoscopy 2002;34:2-12.
22. Bryson HM, Fulton BR, Faulds D. Propofol: an update of its use in anaesthesia and conscious sedation. Drugs 1995;50:513-559.
23. Reimann FM, Samson U, Derad I, Fuchs M, Schiefer B, Stange EF. Synergistic sedation with low-dose midazolam and propofol for colonoscopies. Endoscopy 2000;32:239-244.
24. Seifert H, Schmitt TH, Gültekin T, Caspary WF, Wehrmann T. Sedation with propofol plus midazolam versus propofol alone for interventional endoscopic procedures: a prospective, randomized study. Aliment Pharmacol Ther 2000;14:1207-1214.
25. Jung M, Hofmann C, Kiesslich R, Brackertz A. Improved sedation in diagnostic and therapeutic ERCP: propofol is an alternative to midazolam. Endoscopy 2000;32:233-238.
26. Hall RC, Zisook S. Paradoxical reactions to benzodiazepines. Br J Clin Pharmacol 1981;11 Suppl 1:99S-104S.
27. Silva L, DeLima L, Warren M, Mehta M, Maliakkal RJ. Assessment of level of sedation during gastrointestinal endoscopies: correlation between bispectral index and a trained observer [abstract]. Anesthesiology 1997;87:A495.
28. Silva L, Mehta M, DeLima LGR, Maliakkal RJ, May WL. Bispectral index: an objective method to monitor level of sedation during endoscopy [abstract]. Anesth Analg 1997;84:S265.