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Bispectral index during epidural puncture predicts anterograde amnesia in patients given midazolam premedication

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Abstract
Purpose. We hypothesized anterograde amnesia could be predicted by the bispectral index (BIS) during epidural puncture in patients premedicated with intramuscular midazolam.
Methods. We investigated 64 consecutive patients undergoing gynecological laparotomy under general anesthesia combined with epidural anesthesia. Midazolam (5 mg) was administered intramuscularly at 15 min before arrival at the operating room. The anesthesiologist informed the patient of the operating room number after evaluating her using the Observer's Assessment of Alertness and Sedation (OAA/S) scale. A BIS probe was then attached to the patient's forehead while she was in the lateral position for epidural puncture. Another anesthesiologist interviewed the patient on the day after surgery and asked her the operating room number and whether there was recall of pain. Group A comprised patients with no recall of the room number and no recall of pain during epidural puncture and group R comprised patients who remembered both the room number and the pain. Patients recalling only the room number or the pain were excluded.
Results. Forty patients were classified as group A and 20 as group R. Four patients remembered only the room number and they were excluded. There were significant differences in body weight, OAA/S scale on arrival at the operating room, and average BIS and electromyogram (EMG) values during epidural puncture between the two groups. These four parameters were entered into a multiple logistic regression model for multivariate analysis. The analysis identified the BIS value as the only independent predictor of complete amnesia during epidural puncture.
Conclusion. BIS assessment during epidural puncture is informative for the anesthesiologist to predict amnesia following midazolam premedication.

Key words Bispectral index · Amnesia · Epidural puncture · Midazolam

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Introduction

The bispectral index (BIS) is widely used to prevent intraoperative recall due to inadequate anesthesia [1], as evaluation of the depth of general anesthesia by BIS monitoring is more objective than evaluation with classical indicators such as blood pressure, heart rate, and the size of the pupils. The Observer's Assessment of Alertness and Sedation (OAA/S; Table 1) scale similarly evaluates awake patients under light sedation with midazolam [2], a drug that can induce anterograde amnesia [3–5]. The OAA/S scale was reported to be clinically superior to BIS assessment for patients sedated with nitrous oxide during epidural anesthesia [6], but evaluation with the OAA/S scale can be influenced by an anesthesiologist's bias derived from an opinion of the patient's preoperative characteristics. The amnesia exists between the awake state and loss of consciousness [7], and often occurs even in patients who respond readily to their name spoken in a normal tone. We hypothesized that amnesia could be detected by BIS monitoring, and that the BIS value during epidural puncture could inform the anesthesiologist of pain in the patient.

Methods

The study protocol was approved by the Human Ethics Review Committee of Kansai Denryoku Hospital and a signed consent form was obtained from each subject. We investigated 64 consecutive, American Society of Anesthesiologists (ASA) physical status I-II patients, aged 30 to 60 years, who underwent gynecological laparotomy during the period from July 2006 to December 2007 at Kansai Denryoku Hospital. A premedication dose of intramuscular midazolam (5 mg) was administered 15 min prior to arrival in the operating room (OR). The anesthesiologist in charge evaluated the

Table 1. Observer's assessment of alertness and sedation (OAA/S) scale [2]

Score	Response
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly or repeatedly
2	Responds only after mild prodding or shaking
1	Does not respond to mild prodding or shaking
0	Does not respond to noxious stimulus

patient according to the OAA/S scale. The anesthesiologist also informed the patient of the OR number (language recall). A BIS probe (BIS XP A-2000; Aspect Medical System, Norwood, MA, USA) was then attached to the patient's forehead while in the lateral decubitus position for epidural puncture. Nurses helped patients to maintain the lateral decubitus position with fully flexed legs when patients could not keep the correct position by themselves. An 18-gauge Tuohy epidural needle was inserted after local anesthesia was performed using 20 mg lidocaine. An epidural catheter was placed at the Th12/L1 or L1/L2 interspace. It was confirmed by administering a test dose of 20 mg lidocaine that the epidural catheter was not located in the subarachnoid space. General anesthesia was induced with fentanyl 100–200 μg, propofol 1.5–2.0 $mg \cdot kg^{-1}$, and sevoflurane 3%–5%. Vecuronium bromide 0.1 $mg \cdot kg^{-1}$ was administered for tracheal intubation. Anesthesia was maintained with sevoflurane 1.5%–3%, fentanyl, vecuronium bromide, and epidural ropivacaine administered at 12.5–25 $mg \cdot h^{-1}$. Nitrous oxide was not used during surgery, and droperidol 1.25 mg was administered to prevent postoperative nausea and vomiting at the end of surgery. The day after the surgery, another anesthesiologist, a different person from the one anesthetizing the patient, interviewed the patient and asked her for the operating room number (language recall) and for recall of pain during the epidural puncture (unpleasant experience).

Sixty-four patients treated as described above were divided into two groups according to the recall of room number and pain during the epidural puncture: group A (amnesia group) comprised patients with no recall of the room number and no recall of pain during the epidural puncture, and group R (recall group) comprised those patients who remembered both the room number and the pain. Patients recalling only the room number or the pain were excluded from this study. We compared the following variables in the two groups: (1) preoperative demographic data and intraoperative factors; (2) OAA/S scale before BIS monitoring; (3) mean BIS value on arrival in the OR and at local anesthesia; and (4) average BIS ($BIS_{av.}$) and electromyogram ($EMG_{av.}$) during epidural puncture with a Tuohy epidural needle. The mean BIS and EMG values for 1 min were derived using a printer attached to the BIS monitor, and the $BIS_{av.}$ and $EMG_{av.}$ values were calculated from the sum of the mean values for the whole duration time of epidural puncture divided by the duration time.

Normality (Kolmogorov–Smirnov) and equal-variance tests were applied to all data. If these tests confirmed a normal data distribution, Student's *t*-test was used to compare groups, with the results expressed as means ± SD. When the data were not normally distributed, the Mann-Whitney *U*-test was used and the results were expressed as median values (interquartile ranges). The χ^2 and Fisher's exact tests were also used to compare category data from the two groups. When the analysis flagged a significant difference between groups, power analysis was performed and the sample size was evaluated. Variables associated with anterograde amnesia during epidural puncture (e.g., body weight, OAA/S scale, $BIS_{av.}$, and $EMG_{av.}$), were entered into a multiple logistic regression model for multivariate analysis to identify independent predictors. The odds ratio, 95% confidence intervals (95% CI), and *P* values were calculated for each predictor in the final model. A difference was considered statistically significant when the *P* value was less than 0.05.

Results

Forty patients were classified as group A and 20 as group R (Table 2). There was no significant difference between groups A and R in the time interval between administration of midazolam and the first assessment of BIS value (28.5 ± 4.4 vs 28.6 ± 3.9 min; group A vs group R). Four patients were excluded from this study. All patients in group A could perform knee-bending after the epidural procedure in spite of complete amnesia, except for 1 patient, whom a nurse helped to keep the lateral position. No patients complained about paresthesia during epidural puncture and no patients remembered paresthesia as recall. There were significant differences between groups A and R in body weight, median values of OAA/S scale, $BIS_{av.}$, and $EMG_{av.}$. The power (defined

Table 2. Comparison of perioperative clinical variables between groups A and R

	Group A (n=40)	Group R (n=20)
Age (years)	42 ± 8	43 ± 7
Body weight (kg)	53.5 ± 7.2	62.3 ± 9.9**
Diagnosis		
Benign illness (e.g., myoma, ovarian cyst; %)	88	90
Malignant tumor (%)	12	10
OAA/S scale on arrival in the OR	4 (4)	5 (4) *
Percentage of patients with OAA/S scale 5 on arrival in the OR (%)	23	60
Sp_{O_2} on arrival in the OR (%)	98 (97)	99 (97.5)
BIS on arrival in the OR	89.4 ± 7.0	92.8 ± 6.5
BIS at local anesthesia	85.8 ± 6.9	91.5 ± 5.1**
$BIS_{av.}$ during epidural puncture	86.4 ± 6.1	92.6 ± 4.4****
$EMG_{av.}$ during epidural puncture (dB)	42.9 ± 4.5	48.2 ± 4.7***
Lateral position for epidural puncture (min)	14 (10)	14 (10)
Induction dose of propofol ($mg \cdot kg^{-1}$)	1.5 ± 0.3	1.5 ± 0.3
Total intraoperative fentanyl (μg)	200 (100)	200 (150)
Duration of surgery (min)	140 (107.5)	140 (107.5)

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$;**** $P < 0.0001$
Values are means±SD or medians (interquartile ranges)
OAA/S scale, Observer's Assessment of Alertness and Sedation (OAA/S) scale; EMG, electromyogram; BIS, bispectral index; $BIS_{av.}$ and $EMG_{av.}$, mean BIS and EMG values for the whole duration of epidural puncture with Tuohy epidural needle

Table 3. Predictors of amnesia / recall during epidural puncture

Factor	Odds ratio	95% CI	P value
Body weight (kg)	1.092	0.983–1.214	0.101
OAA/S scale	2.371	0.521–10.792	0.264
$BIS_{av.}$	1.306	1.031–1.654	0.026
$EMG_{av.}$ (dB)	1.134	0.923–1.393	0.231

OAA/S scale, Observer's Assessment of Alertness and Sedation (OAA/S) scale; EMG, electromyogram; BIS, bispectral index; $BIS_{av.}$, $EMG_{av.}$, mean BIS and EMG values for the whole duration of epidural puncture with Tuohy epidural needle; CI, confidence interval
Odds ratio of $BIS_{av.}$ indicates rate of recall during epidural puncture becomes 1.3 fold when BIS values increases at one point

as the ability of a test to detect an effect given that the effect actually exists) of body weight, $BIS_{av.}$, and $EMG_{av.}$ was 0.931, 0.954, and 0.982, respectively. Nine patients in group A were judged as OAA/S scale 5 by an anesthesiologist, although the BIS value in 6 of these patients was less than 90. We considered body weight, OAA/S scale, $BIS_{av.}$, and $EMG_{av.}$ as important predictors of complete amnesia during epidural puncture. These four factors were subsequently entered into multiple logistic regression analysis, which identified $BIS_{av.}$ as the only critical independent predictor of complete amnesia during epidural puncture (Table 3).

Discussion

Recall of pain during epidural puncture is an unpleasant experience for patients, especially for the nervous young woman, and, in postoperative patient interviews, epidural anesthesia was shown to be one of the anesthetic factors with which most patients were dissatisfied [8]. These patients may tend to avoid epidural anesthesia in any future surgery. Amnesia during an epidural procedure, induced by using sedative drugs, is therefore desirable in some patients. This is the first report describing the efficacy of BIS monitoring during epidural puncture to predict anterograde amnesia.

The OAA/S scale is superior to the BIS value for assessing the state during deep sedation with midazolam. However, deep sedation can make it impossible to place patients in the lateral decubitus position for epidural puncture. Consequently, an optimal sedative level for the patient was considered to be a level moderate enough to enable the patient to take a suitable lateral decubitus position with flexed legs by themselves and strong enough to prevent the recall of pain during epidural puncture. This sedative level probably shows as an OAA/S scale 4, although it is difficult for an anesthesiologist to distinguish between OAA/S scales 4 and 5 in some patients at a glance, and evaluation of the OAA/S scale can be influenced by an anesthesiologist's bias derived from an opinion of a patient's preoperative characteristics. In the present study, six patients in group A were assessed as OAA/S scale 5, despite the BIS value in these same patients being less than 90. Our results demonstrated that estimating BIS values during epidural puncture was more informative and objective than using the OAA/S scale for anesthesiologists in predicting amnesia in a surgical patient. Hence, BIS monitoring should be performed when a moderate sedative level is desirable.

Our hypothesis is supported by the findings of Glass et al. [9], who reported that 50% of healthy volunteers

demonstrated a complete lack of recall at BIS values ranging from 84 to 86; other reports demonstrated that amnesia with midazolam existed between BIS values of 80 and 90 [10,11]. Baker et al.[7] have shown that propofol induces amnesia in patients with a BIS of 82. It is interesting that our mean BIS value in group A was similar to previous reports, though we investigated a different kind of recall, i.e., recall of pain during epidural puncture, from that in other studies, i.e., recall of a picture, dental pulp stimulation, and cardioversion [7,9–11]. Electroencephalograms (EEGs) may also be useful for predicting amnesia because EEG studies using midazolam identified that a rise in spectral power in the Beta band (14 to 30 Hz) and a concomitant decrease in the Alpha band (8 to 13 Hz) correlated with the onset of amnesia [12]. However, when sedative drugs are administered intravenously and patients lose consciousness quickly, a significant decrease in BIS usually indicates that the amnesic point around BIS 85 has passed already [7]. On the other hand, amnesia can be detected exactly when intramuscular midazolam is administered for a slow effect, such as premedication. We therefore consider that the BIS value is valuable for evaluating both amnesia and the sedative level with intramuscular midazolam premedication. Anesthesiologists should target a BIS value below 90 to the appropriate sedative level if a patient requests amnesia during epidural puncture.

After intramuscular administration, midazolam 5 mg was absorbed with the peak serum concentration being achieved at around 30 min [13,14]. The time interval between the administration of midazolam and the first assessment in our study was approximately 30 min and BIS values were gradually reduced after the first assessment on arrival in the OR. Therefore, the peak concentration of midazolam was achieved during epidural puncture in almost all the patients. The sedation level was closely related to the serum midazolam concentration [13], so that the patient was considered to be sedated at the deepest level during epidural puncture. We considered 5 mg intramuscular midazolam was free from side effects such as respiratory depression, and all the patients in our study were able to be in conversation with an anesthesiologist and perform knee-bending during epidural puncture. Intramuscular midazolam at 0.08–0.1 $mg \cdot kg^{-1}$ was recommended for young adult patients as anesthetic premedication [15]; however, a fixed dose of midazolam was administered to all our patients. We have not used more than 5 mg intramuscular midazolam as premedication. Hence, we used a fixed dose of midazolam to avoid side effects at the deepest sedation level before patients' arrival in the OR. It may be not surprising that bigger patients were less sedated and more likely to recall epidural puncture.

When the BIS was monitored in an awake patient, the influence of EMG was not ignored. Our study was limited in that the EMG values were higher than expected in all patients, and were significantly higher in group R than in group A. Most of the overlap of BIS values between the two groups existed at values of more than 90 and this was closely related to the influence of EMG, because the BIS values are significantly increased by electromyographic activity [16]. But EMG itself was reported to be useful for detecting both loss of and return of consciousness [17] and our result showed that EMG could also be a useful predictor of amnesia, in combination with the BIS value.

The BIS value is primarily used to prevent intraoperative recall due to inadequate anesthesia, but BIS assessment during epidural puncture is also informative for anesthesiologists, and enables them to better predict amnesia following midazolam premedication. We conclude that BIS should be monitored if a patient requests amnesia during epidural puncture.

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