J Anesth (2009) 23:182–187
DOI 10.1007/s00540-008-0722-3

Journal of
Anesthesia

Low bispectral index values following electroconvulsive therapy associated with memory impairment

Toshiya Koitabashi, Tomoko Oyaizu, and Takashi Ouchi

Department of Anesthesiology, Ichikawa General Hospital, Tokyo Dental College, 5-11-13 Sugano, Ichikawa 272-8513, Japan

Abstract
Purpose. It has been reported some patients have opened eyes with low bispectral index (BIS) values immediately following electroconvulsive therapy (ECT). We investigated the time course of the recovery from amnesia and BIS values.
Methods. Five patients with depression requiring repeated ECT procedures were enrolled. The patients were asked to recall an object presented prior to anesthesia at four specific points (prior to induction, upon regaining consciousness following ECT, when they returned to their ward, and when their BIS values had returned to pre-anesthetic levels). BIS data were recorded continuously until BIS values returned to the pre-anesthetic levels at their ward. The area under a receiver-operating characteristic (ROC) curve was used to detect associations between the BIS values and disturbance of memory function.
Results. A total of 41 ECT stimuli were administered. After returning to their ward, patients generally fell asleep, with BIS values of between 50 and 70, and they woke up 1–2 h later. All the patients could recall the presented object prior to anesthesia and when the BIS values had returned to pre-anesthetic levels. The area under the ROC curve for the detection of memory disturbance was 0.902.
Conclusion. The present study demonstrated a high frequency of patients falling asleep and the frequent occurrence of prolonged periods of low BIS values following ECT. The results of memory testing showed that ECT procedures resulted in amnesia. The ROC curve findings suggest a strong association of memory disturbance with BIS values. In conclusion, patients generally fell asleep, with low BIS values, for 1–2 h after ECT, and a prolonged period of impairment of memory formation was associated with low BIS values.

Key words Amnesia · BIS · ECT · Memory impairment

Address correspondence to: T. Koitabashi
Received: August 27, 2008 / Accepted: November 17, 2008

Introduction

Electroconvulsive therapy (ECT) is used to treat a number of major affective disorders, particularly medication-resistant major depression. The therapeutic efficacy of ECT may be related to the duration of the induced seizure [1] or to the occurrence of a brief period of electrocerebral silence following the induced seizure [2]. Short-acting anesthetics, such as methohexital, thiopental, and propofol, are frequently used to provide general anesthesia for ECT. However, excessive dosing of these agents can reduce the duration of the induced seizure and possibly compromise the efficacy of the ECT [1,3–5]. Therefore, it is important to adjust the hypnotic state of the patient just before the electrical stimulus to be able to induce the appropriate duration of electrically induced seizure.

The bispectral index (BIS) is an electroencephalogram-derived parameter that reflects the level of hypnosis in anesthetized patients [6]. The BIS correlates well with drug-induced memory impairment and the loss of consciousness induced by anesthetic and sedative agents [7]. Nishihara and Saito [1] reported that seizure duration had a positive correlation with the BIS value immediately before the electrical stimulus, indicating that the BIS may be useful to prevent excessive cerebral suppression just before ECT. In other investigations, some patients with low BIS values have opened their eyes and regained consciousness immediately following ECT, suggesting that the BIS may not be an accurate predictor of awakening following ECT [1,4,5,8]. A period of profound amnesia is common following ECT, presumably due to postictal alterations in memory function. To date, the time course of the recovery from amnesia and BIS values have not been studied in patients receiving ECT.

In the present study, we hypothesized that BIS values would correlate with measures of memory function following ECT procedures. A secondary objective of this

study was to determine the time course of the recovery of BIS values following ECT.

Patients, materials, and methods

The clinical study was performed with the approval of the Institutional Review Board (IRB) and Human Research Committee, and written informed consent was obtained from the patients. Five adult patients with drug-resistant depression requiring a series of ECT procedures were involved in this study. Prior to the ECT procedures, the patients were receiving various regimens of benzodiazepines, antidepressants, or both, including diazepam, imipramine, amoxapine, amitriptyline, fluvoxamine, and milnacipran, which were continued during and after the ECT procedures.

Anesthesia monitoring for the ECT procedures included noninvasive blood pressure, electrocardiogram, pulse oximetry, and BIS. All monitors were applied when the patients entered the operating theater and values were recorded throughout the procedure. BIS monitoring utilized a A2000 BIS XP monitor (version 4.0; Aspect Medical Systems, Newton, MA, USA) and a BIS Sensor XP applied on the patient's forehead as recommended by the manufacturer. The impedance of each electrode was kept below 5 k ohm, and BIS data were downloaded and recorded continuously by a computer. The baseline BIS values were obtained 3 min after quiet and eye-closed conditions. Following preoxygenation, anesthesia was induced with intravenous thiopental (3 $mg \cdot kg^{-1}$) and suxamethonium (1 $mg \cdot kg^{-1}$). A tourniquet was inflated on one extremity to permit assessment of motor seizure activity. Patients were ventilated with 100% oxygen with a face mask. The ECT stimulus was delivered when the BIS value was between 50 and 60, via bitemporal electrodes set at 110 V and maintained for 5–7 s (Sakai CS-1 apparatus; Sakai Medical Instruments, Tokyo, Japan). The duration of each induced seizure was determined by both evoked motor activity and by visual inspection and monitoring of the electroencephalogram. Following the ECT procedure, patients were discharged from the operating theater when they met the discharge criteria (stable hemodynamics, spontaneous breathing without any support, and appropriate muscle strength). When they returned to their ward, BIS monitoring was continued and the results were recorded until BIS values had returned to the pre-anesthetic levels.

Prior to preoxygenation, patients were asked to recognize common household objects (such as a cup, watch, key, light, compact disc, or pen) presented visually. The patients were subsequently asked to recall the presented object at four specific time points: (1) immediately prior to the administration of thiopental, (2) upon regaining consciousness and opening the eyes following ECT, (3) when they returned to their ward, and (4) when their BIS values had returned to pre-anesthetic levels. Prior to discharge from the operating theater, patients were asked to perform a handshake to assess muscle strength. At time points 3 and 4, patients were also assessed for memory of the handshake. The time line for the study protocol is illustrated in Fig. 1.

Statistical analysis

Data values are presented as means ± SD. All statistical analyses were undertaken using SPSS software for Windows (version 16.0; SPSS, Chicago, IL, USA). Statistical analysis for the changes in BIS values was performed using repeated-measures analysis of variance (ANOVA) and post-hoc Bonferroni test. Assessments of the nonlinear association between the BIS values and the probability of disturbance of memory function were accomplished using the logistic regression procedure, which estimated the probability of a binary

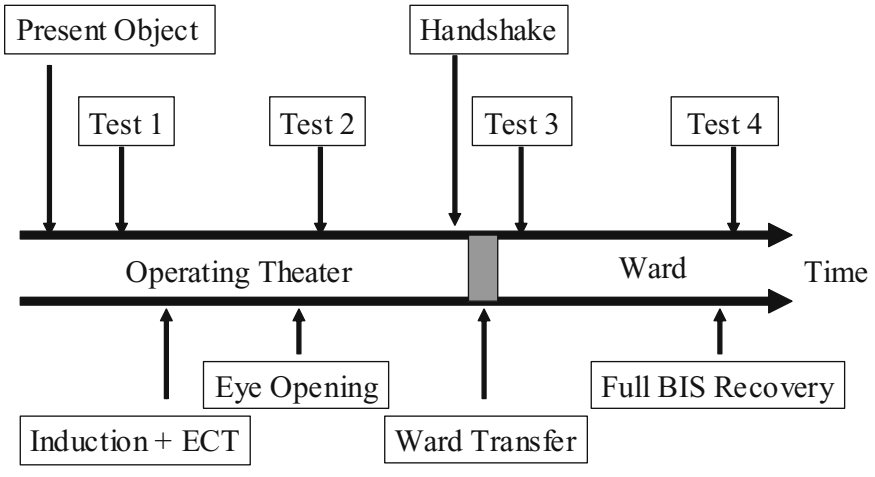

Fig. 1. This diagram shows the timing of presentation of specific items and subsequent memory assessments around the electroconvulsive therapy (*ECT*) procedure in this study. A household object was presented prior to anesthesia induction, and a handshake was performed immediately before the patient was transferred to the ward. Ability to recall the household object was assessed twice in the operating theater and twice in the ward. Ward assessments also tested for recall of the handshake. *BIS*, Bispectral index

"yes/no" response. The relationship between the BIS values and memory disturbance was analyzed by receiver-operating characteristic (ROC) curves, in which the area under the curve (AUC) was calculated as described elsewhere [9]. The ROC curve was determined by plotting the sensitivity against 1–specificity, and discriminating the power of the BIS values. The area under the ROC curve summarizes the predictive power of the index to achieve a high specificity at any given sensitivity. An area above 0.5 indicates that the measurement is predictive, and a measurement with 100% accuracy would have an area of 1.0. However, an area under the ROC curve which is 0.5 indicates that there is no predictive power. Cutoff points were optimized from the ROC curves to maximize the sum of sensitivity and specificity. A P value less than 0.05 was considered statistically significant.

Results

A total of 41 ECT stimuli in five patients (age, 21, 34, 44, 50, and 73 years) were administered without any adverse events. However, during one treatment, the ECT stimulus delivered to a 73-year-old patient failed to induce a seizure. Consequently, data from 40 ECT procedures were included in the analysis. The depressive symptoms in all patients were alleviated during the course of the ECT procedures.

The pre-anesthetic baseline BIS value was 94 ± 7. The BIS prior to the ECT electrical stimulus was 56 ± 11 ($P < 0.05$ compared to baseline). Patients were awake and responsive to verbal commands 469 ± 138 s after the ECT stimulus, with a BIS value of 61 ± 17 ($P < 0.05$ compared to baseline).

After returning to their ward, the patients generally fell asleep and spontaneously woke up 96 ± 28 min after the ECT stimulus. During these sleeping periods, the BIS values were maintained between 50 and 70. A typical BIS trend is illustrated in Fig. 2. Upon awakening in the ward, the BIS value was 86 ± 4.

The results of memory testing at the four time points noted above are presented in Table 1. All patients could recall the presented object when queried prior to the administration of thiopental. Patients did not recall the

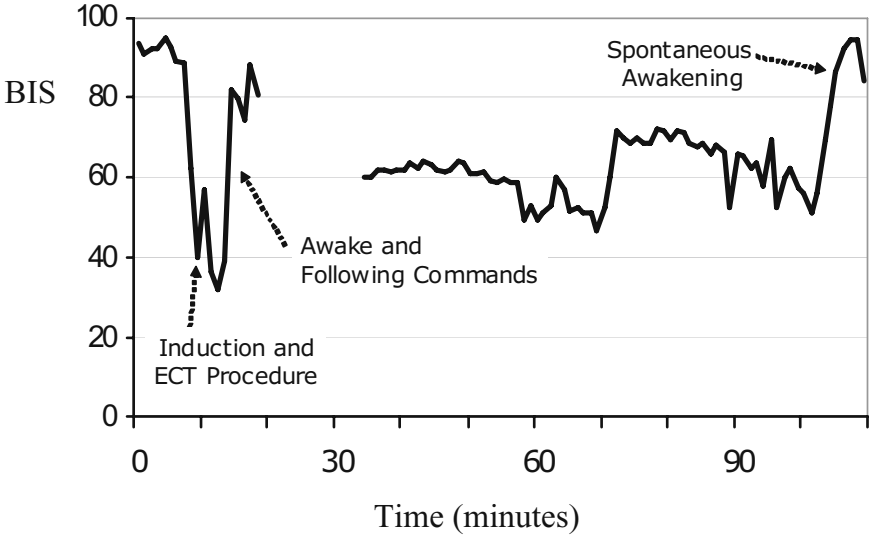

Fig. 2. Typical trend of BIS values observed in study patients during and following the ECT procedure. A rapid decrease in the BIS is seen with the induction of anesthesia immediately prior to the ECT procedure (*first arrow on the left*). After the ECT, the patient was awake and following commands, with a BIS value of approximately 60. There is a gap in the recording during transfer from the operating theater to the ward. Upon return to the ward, this patient fell asleep and awakened approximately 75 min later, with a BIS value of 86

Table 1. Memory assessments before and after ECT

Patient no. (age; years)	Pre-ECT	Eyes open	Ward arrival		Full BIS recovery	
	Object	Object	Object	Handshake	Object	Handshake
1 (21)	9/9[a]	0/9	0/9	0/9	9/9	0/9
2 (34)	9/9	0/9	0/9	0/9	9/9	0/9
3 (44)	7/7	0/7	0/7	0/7	7/7	0/7
4 (50)	7/7	0/7	0/7	0/7	7/7	0/7
5 (73)	8/8	0/8	0/8	0/8	8/8	0/8

The data table lists four memory test points for each patient and each memory assessment
ECT, electroconvulsive therapy; *BIS*, bispectral index
[a]At each time point, the number of correct recalls of the memory challenge (the presented object and/or the handshake) out of the number of memory assessments is noted

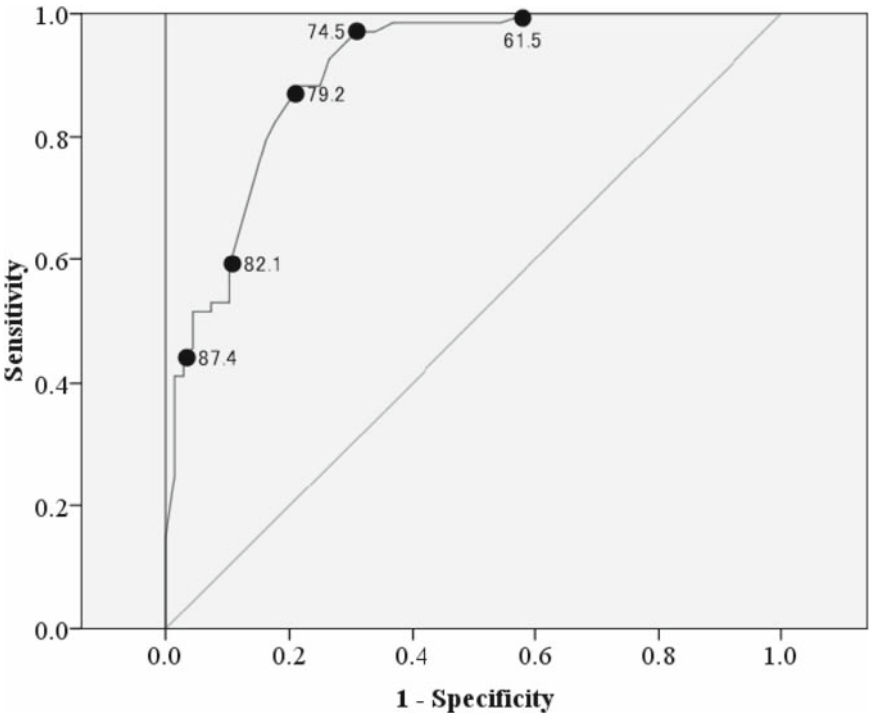

Fig. 3. The disturbance of memory function evaluated by a receiver-operating characteristic (ROC) curve. The ROC curve was determined by plotting the sensitivity against 1–specificity, and discriminating the power of the BIS values. The area under the ROC curve value is 0.902, demonstrating that the BIS was a significant predictor of the disturbance of memory function. Cutoff was obtained from ROC curves to maximize the sum of sensitivity and specificity. A BIS cutoff value of 79.2 was obtained from the ROC curve, and the sensitivity and specificity at this point were 88.2% and 79.4%, respectively

presented object upon regaining consciousness following ECT or after arrival in their ward. All patients could recall the presented object when the BIS values returned to pre-anesthetic levels. None of the patients recalled their operating theater discharge handshake when they returned to their ward nor when they woke up and BIS values had returned to pre-anesthetic values. No patients reported explicit memories during ECT or during the post-ECT sleeping periods. The ROC curve is shown in Fig. 3. Logistic regression analysis demonstrated that the BIS was a significant predictor of the disturbance of memory function, with the area under the ROC curve being 0.902 (95% confidence intervals, 0.852–0.953). A BIS cutoff value of 79.2 was obtained from the ROC, and the sensitivity and specificity at this point were 88.2% and 79.4%, respectively.

Discussion

BIS monitoring provides anesthesiologists with information of the hypnotic levels of general anesthesia and can indicate loss of consciousness as well as the regaining of consciousness following anesthesia [6,7]. Patients with advanced neurologic disease have been observed to have low BIS values at baseline. However, it has been reported that baseline BIS values exceeded 94 in 90% of depressed patients despite the presence of moderate-to-severe depressive symptoms [4]. Similarly, we observed that, despite our patients' major depressive illnesses and requisite medical therapy, their baseline BIS values were in the normal range. This evidence supports the ideas that cortical function may not be so impaired in depressed patients and that BIS values are reliable in depressed patients.

We found that patients were awake and followed verbal commands following ECT procedures, with a BIS value of 61 ± 17. In most general anesthetic procedures, BIS values increase during emergence and the regaining of consciousness, and patients typically follow commands when their BIS values are above 80. However, the time courses of BIS values following ECT procedures we observed were different from the usual post-anesthetic pattern, and are consistent with other reports. White et al. [4] reported that patients awoke with BIS values of 50 ± 16 following ECT procedures performed under etomidate anesthesia. After ECT procedures performed under propofol anesthesia, a similar BIS pattern was also reported [1]. Patients in the postictal state often display slow delta EEG waves even after they have regained consciousness [8]. Gunawardane and colleagues [8] have demonstrated that one of the subparameters used to calculate the BIS, "SynchFastSlow", remains low and contributes to the low BIS values observed at awakening following ECT procedures.

We observed a high frequency of patients falling asleep, and the frequent occurrence of prolonged periods of low BIS values. We could not find any other studies which measured BIS values for a prolonged period following ECT. Therefore, the current study appears to be the first report describing the time course of the recovery of BIS values following ECT.

Amnesia can occur when any one of the components of memory function, such as memorization, retention, and retrieval is impaired. Our patients recalled presented objects prior to the induction of anesthesia, indicating both intact memory function and the usual capacity for attention. However, these patients could not recall the same presented objects when they were assessed after regaining consciousness and responding to commands in the operating theater, nor could they recall the objects upon returning to their ward. These findings—which occurred when BIS values were low—suggest that the ECT procedures produced a sustained impairment of the component of memory retrieval. In addition, the failure of patients to recall the handshake administered early in the postictal period suggests that the memorization and/or retention components of memory formation were also impaired during the post-ECT period. During this period, low BIS values were observed. The area under the ROC indicated that BIS values had high sensitivity and specificity with respect to the ECT-induced memory impairment. The BIS cutoff value from the ROC (showing maximal sensitivity with maximal specificity) to discriminate between normal memory function and memory disturbance was 79.2. Accordingly, this study has clearly demonstrated that ECT procedures result in the impairment of two or possibly all three components of memory function for 1–2 h following the procedure. We conclude that low BIS values, below 79.2, following ECT procedures are consistent with the impairment of higher brain functions, including memory formation.

We selected thiopental to induce anesthesia in the present study. In Japan, neither etomidate nor methohexital are available as induction agents. Although recent studies have demonstrated that both systemic and cerebral hemodynamics during ECT are more stable under propofol anesthesia than under barbiturate anesthesia [3], the seizure duration tends to be shorter under propofol anesthesia. In fact, in 40 of our 41 ECT procedures, an induced-seizure was elicited, and all patients improved.

This observational study can be criticized because only a small series of patients were studied and the state of the patients' brains changed progressively during the course of the ECT. However, there were no inter- or intra-patient differences with regard to the results for memory function and the time course of the BIS values following ECT. In addition, the ROC findings suggest a strong association of memory disturbance with BIS values. Therefore, we considered that a total of 41 ECT procedures would be appropriate to draw a significant conclusion.

The next issue is whether the second drop in the BIS after emergence from anesthesia is particular to ECT, because infants usually fall asleep in the ward after emergence from anesthesia in the operating theater. Thus, it is possible that the use of a control group would clarify whether this phenomenon is specific to patients who have received ECT. However, it is difficult to enroll patients or volunteers who will agree to be administered thiopental alone without a surgical procedure. On the other hand, some patients having procedures other than ECT fall asleep following extubation, although their EEG pattern is not the slow delta waves which are seen during profound anesthesia. Their EEG is only a little suppressed by the residual effects of the general anesthetic. However, patients in the postictal state often display slow delta EEG waves even after they have regained consciousness. Therefore, the EEG pattern following anesthesia is fundamentally different in patients with and without ECT. Presumably, awakening occurs following a sufficient decrease in the effect-site concentration of thiopental after ECT. We consider that patients in the postictal state cannot maintain consciousness owing to the severe cortical suppression, which requires 1–2 h for full recovery. Therefore, we think that a conclusion can be drawn regarding the results of this study without the need for a control group. Moreover, it may be of concern that the patients may have been receiving benzodiazepines before the ECT, as drugs of this class are known to have prolonged effects on antegrade amnesia. However, the memory function of the patients was intact before the ECT, and the amnesia continued for approximately 2 h after the ECT and subsequently recovered, indicating no effects of the pretreatment agents on memory function throughout the study period.

In our patients, we observed eye opening and response to verbal commands approximately 7 min after an ECT procedure. Despite the patients' ability to respond to commands, we simultaneously documented that higher brain functions such as memory were substantially impaired. We also observed a prolonged period of low BIS values during the impairment of memory function. We postulate that the seizure induced by ECT produced prolonged EEG changes, as reflected by low BIS values, and fundamentally these patients had a different state of consciousness compared with that in most patients following general anesthesia. Interestingly, in one treatment session for one of our patients, a seizure could not be induced. This patient awoke from anesthesia at a BIS value of 88. His memory of the presented object was intact at that time point and at subsequent time points following anesthesia. Accordingly, we believe that the induced-seizure activity is responsible for the prolonged period of memory impairment. We conclude that, following ECT procedures, a prolonged period of low BIS values is indicative of ongoing impairment of memory formation that resolves 1–2 h after the ECT procedure.

References

1. Nishihara F, Saito S. Pre-ictal bispectral index has a positive correlation with seizure duration during electroconvulsive therapy. Anesth Analg. 2002;94:1249–52.
2. Langer G, Neumark J, Koinig G, Graf M, Schonbeck G. Rapid psychotherapeutic effects of anesthesia with isoflurane (ES narcotherapy) in treatment-refractory depressed patients. Neuropsychobiology. 1985;14:118–20.
3. Nishihara F, Saito S. Adjustment of anaesthesia depth using bispectral index prolongs seizure duration in electroconvulsive therapy. Anaesth Intensive Care. 2004;32:661–5.
4. White PF, Rawal S, Recart A, Thornton L, Litle M, Stool L. Can the bispectral index be used to predict seizure time and awakening after electroconvulsive therapy? Anesth Analg. 2003;96:1636–9.
5. Ochiai R, Yamada T, Kiyama S, Nakaoji T, Takeda J. Bispectral index as an indicator of seizure inducibility in electroconvulsive therapy under thiopental anesthesia. Anesth Analg. 2004;98: 1030–5.
6. Sebel PS, Lang E, Rampil IJ. A multicenter study of bispectral electroencephalogram analysis for monitoring anesthetic effect. Anesth Analg. 1997;84:891–9.
7. Glass PS, Bloom M, Kearse L. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology. 1997;86:836–47.
8. Gunawardane PO, Murphy PA, Sleigh JW. Bispectral index monitoring during electroconvulsive therapy under propofol anaesthesia. Br J Anaesth. 2002;88:184–7.
9. Hanley JA. Receiver operating characteristic (ROC) methodology: the state of the art. Crit Rev Diagn Imaging. 1989;29:307–35.