Use of the Bispectral Index to Predict Recovery of Consciousness in Patients with Spontaneous Intracerebral Hemorrhage After Surgical Hematoma Evacuation: A Prospective Cohort Study

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Our study aimed to test the predictive value of the bispectral index (BIS) for the post-operational consciousness recovery in patients undergone hematoma evacuation due to spontaneous intracerebral hemorrhage (ICH).

Material/Methods: In this prospective cohort study, we enrolled adult spontaneous ICH patients after surgical hematoma evacuation who did not recover consciousness on the first postoperative day. After patient enrollment, the BIS was continuously monitored for 12 hours, and the motor response on the Glasgow Coma Scale (GCS-M) was evaluated. The patients were followed up for 30 days and divided into a consciousness recovery group and a nonrecovery group. Receiver operating characteristic curve analysis was performed to investigate the predictive values of the BIS, GCS-M and ICH score on the consciousness recovery. The area under the curve (AUC) and 95% confidence interval (95%CI) were calculated. During the 12-hour monitoring period, the peak BIS value after GCS-M stimulation was used for ROC analysis.

Results: Of the 55 enrolled patients, 19 patients recovered consciousness, and 36 patients did not. The BIS value of the consciousness recovery group was significantly higher than that of the nonrecovery group (P<0.001). For consciousness recovery prediction, the AUC (95%CI) of the BIS values after external stimulation was 0.97 (0.91–1.00), which was superior to the GCS-M (0.75 [0.59–0.91]) and ICH score (0.57 [0.41–0.73]).

Conclusions: Our study demonstrates that BIS might be a potential tool for predicting the consciousness recovery in ICH patients undergone surgical hematoma evacuation.

MeSH Keywords: Cerebral Hemorrhage • Consciousness Monitors • Neurosurgery

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Background

Spontaneous intracerebral hemorrhage (ICH) is a major cause of acute stroke resulting in poor neurological outcomes [1]. The reported 30-day case fatality rates range from 30% to 55%, and more than half of the surviving patients are still severely disabled despite the initial aggressive treatment [2]. The prediction of functional recovery is important for decision-making by healthcare providers and families [3].

For patients with spontaneous ICH, several scoring systems have been introduced to predict functional outcomes, in which comprehensive items are used that mostly include age, level of consciousness, hematoma volume, and location [4]. However, none of these systems can incorporate all potential prognostic factors. This might be the reason why new predicting scores are constantly being developed [4,5].

Early recovery of consciousness is a major issue in ICH patients who have undergone surgical hematoma evacuation [3]. As a quantitative electroencephalogram (EEG) instrument, the bispectral index (BIS) is reported to be a potential predictor of coma after cardiac arrest and traumatic brain injury in addition to other predictive tools for consciousness recovery [6–9]. However, until now, no study has been performed to evaluate the role of BIS in predicting the consciousness recovery in ICH patients after hematoma evacuation.

In the present study, BIS was monitored early in the postoperative period for patients with ICH who did not regain consciousness after surgical hematoma evacuation. Our objective was to assess the predictive value of BIS on consciousness recovery in this patient population.

Material and Methods

The protocol was under the approval of the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China (KY 2015-034-02). Written informed consent was obtained from appropriate substitute decision makers because the patient was unconsciousness when enrolled.

Study design, settings, and routine clinical practices

We conducted this prospective cohort study in a 20-bed neurosurgical intensive care unit (ICU) in a 1100-bed university hospital from January to December 2017. During this study, routine perioperative practice was conducted without any change [10].

Attending neurosurgeons made the diagnosis of spontaneous ICH based on clinical presentation, computed tomography (CT) scans, and carotid angiograms. The decision to evacuate the hematoma was made by the neurosurgeons. In our hospital, the treatment of spontaneous ICH follows the 2015 guidelines recommended by the American Heart Association/American Stroke Association (AHA/ASA) [11]. Generally, the decision of surgical hematoma evacuation depends on cerebellar hemorrhage with neurological deterioration or brain stem compression, lobar ICH with a hematoma volume greater than 30 mL and a cortical surface distance within 1 cm, and a significantly life-threatening mass effect. All procedures were performed under general balanced anesthesia. At the end of the surgery, the anesthesiologist and neurosurgeon discussed the timeline for extubation. Generally, criteria for delayed extubation after hematoma evacuation usually include preoperative consciousness impairment, cerebellar hemorrhage, intraoperative brain swelling, time of surgery more than 6 hours, and severe cardiovascular and respiratory instability during the attempt of emergence. All patients with delayed extubation were transferred directly to the neurosurgical ICU.

General monitoring and treatment policy for secondary insult prevention was followed during the postoperative period. Assisted/controlled mechanical ventilation was performed as needed to regain normoventilation. Normovolemia was obtained by careful volume expansion to a central venous pressure of 3–8 mmHg. Blood pressure (BP) was monitored by an intra-arterial line, and the mean arterial blood pressure (MAP) was maintained at 90–130 mm Hg. Urapidil or calcium channel blockers were used if the systolic BP or MAP was increased above 200 mm Hg or 130 mm Hg, respectively. Analyses of complete blood count, partial thromboplastin time, and international normalized ratio (INR) were performed within 120 minutes since the patients reached the ICU. Fresh frozen plasma and vitamin K were administered to those patients taking warfarin and to those whose INR was above 1.4. Continuous intravenous infusion of propofol and fentanyl was used to treat agitation [12]. We conducted a conventional glucose control scheme in our ICU. Blood glucose levels were monitored at least 4 times a day. A continuous insulin infusion was initiated if the blood glucose concentration measured by the ICU-based blood gas/glucose analyzer exceeded 11.1 mmol/L. Intermittent pneumatic compression was used to prevent deep venous thromboembolism. Unfractionated heparin or low-molecular-weight heparin was not used in the acute phase of ICH in our ICU. Prophylactic anticonvulsants were not routinely used.

CT scans were performed in all patients within 24 hours after being transferred to the ICU. Additional CT scans were obtained based on the patient's clinical condition.

ICU nurses performed and documented neurological examinations every 4 hours and included the Glasgow Coma Scale (GCS), pupil diameter and response, and the presence of focal motor deficits. In endotracheal intubated patients, the motor reacts

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to stimulation in GCS (GCS-M) [13] were precisely evaluated and documented. A verbal order was made to the patient to open eyes or raise hands with a mild tone, and followed by a loud tone. If patients made no response to the loud order, they would be tapped on their shoulders with a verbal order. If the patient could follow the command by the tapping and oral commands, the responses were considered to be positive (GCS-M=6). If the patient did not respond, the investigator would give a GCS-M score according to no response (GCS-M=1), stereotyped extension (GCS-M=2), stereotyped flexion (GCS-M=3), withdrawal flexion (GCS-M=4), and differentiation of pain localization (GCS-M=5).

Study population

All adult patients with delayed extubation after surgical hematoma evacuation for spontaneous ICH were screened daily for study eligibility. A well-trained investigator reviewed the hospital records and assessed the patient's consciousness by the GCS-M at 09: 00 AM on the first postoperative day. Exclusion criteria included: 1) ICH attributed to trauma, hemorrhagic conversion of ischemic stroke, or structural lesions (tumor, aneurysm, arteriovenous malformation, and vessel dissection); 2) epilepsy; 3) do-not-resuscitate (DNR) order provided by the patients or the patients' healthcare surrogates; 4) already recovered consciousness which was indicated by GCS-M=6; and 5) suspected brain death pending confirmation. Brain death was suspected if hypothermia was present (core temperature below 35°C) in the absence of drugs known to depress the central nervous system, if the neurological examination demonstrated the absence of brainstem reflexes, and if spontaneous ventilation was absent [14].

BIS monitoring

After enrollment, the patient was continuously monitored by BIS for 12 hours, during which time GCS-M was assessed every 4 hours by one of the well-trained investigators who was blinded to the BIS monitor. The start time of the GCS-M assessment was documented to identify the influence of GCS-M stimulation on BIS during subsequent offline BIS analysis.

A BIS A-2000 XP monitor (Aspect Medical Systems, Inc., Norwood, MA, USA: Host version 3.31) was used. After the skin preparation by alcohol swabs, a set of BIS™ 4 Electrode Sensor (Aspect Medical Systems, Inc., Norwood, MA, USA: Catalog No 186-0106) was set in accordance with the manufacturer's instruction that one electrode was located on the midline 5 cm above the nose, one electrode laterally and below the first one, the third one above the temporal region behind the eye, and the fourth above and near the eyebrow. A sensor was attached to the forehead of the healthiest cerebral hemisphere, which was identified by CT scan. The BIS monitor was

connected to the sensor via a patient interface cable and a digital signal converter. The electrode impedance was maintained below 5000 Ω to ensure adequate signal quality. BIS values were collected via the RS232 port and saved as a Microsoft Excel file on a computer for offline analysis.

Data collection

Data collected at the study entry included the following: age, gender, previous medical history, presence of intraventricular hemorrhage (IVH), volume and location of hematoma, type of surgery, GCS, time from ictus to surgery, and time from the end of surgery to enrollment (BIS monitoring). The location of the hematoma was classified as in the lobes, basal ganglia or thalamus, cerebellum, and brainstem. The hematoma size was evaluated by using the ABC/2 method [15]. The type of surgery was classified as craniotomy or burr hole, with or without external ventricular drainage (EVD). The ICH score [16] and Acute Physiology and Chronic Health Evaluation (APACHE) II score [17] were calculated. A reoperation due to hematoma enlargement or brain swelling was also documented.

All BIS data were collected for offline analysis as in a previous report [18]. The BIS values were documented every minute in a Microsoft Excel file. Patients were given verbal or physical stimulations during the GCS-M assessment. The start time of the GCS-M assessment was identified. BIS values within 15 minutes before and after the start of the GCS-M assessment were collected. BIS values were included for further analysis if the signal quality index (SQI), which was quantified as the percentage of the first 60 seconds of data used to calculate the BIS, was greater than 75%. The respective peak BIS values before and after GCS-M stimulation were selected. BIS data were reviewed and collected independently by 2 investigators who were blinded to the consciousness status of the patients. The 2 investigators compared their data forms and resolved any discrepancies by consulting the primary investigator. The use of propofol for control of agitation was retrospectively collected from the ICU nursing records.

Patients were followed up for 30 days after enrollment, or until they recovered consciousness or died, on a first come, first served basis. These patients were examined at 09: 00 AM every day. The recovery of consciousness was also evaluated by GCS-M and was defined as command obeying (GCS-M=6). Based on the follow-up results, patients were assigned into the consciousness recovery group (GCS-M=6) or the nonrecovery group (GCS-M=0 to 5).

Statistical analysis

Categorical data were shown as a percentage and analyzed by the χ^2-test. Continuous data were presented as the median

(interquartile range, IQR) and compared using the Mann-Whitney U test. The Wilcoxon signed rank test was used to compare the BIS values before and after stimulation.

The Spearman rank-order correlation analysis was run to investigate the correlation between BIS and GCS-M, and the correlation coefficient (r) was calculated.

A receiver operating characteristic (ROC) curve analysis was used to evaluate the ability of variables (BIS, GCS-M and ICH score) to predict the recovery of consciousness. The area under the curve (AUC) and 95% confidence interval (95%CI) were calculated and tested if the AUC was significantly greater than 0.5. During the 12-hour monitoring period, the peak BIS value after GCS-M stimulation was used for ROC analysis. The AUC for each variable was pairwise compared using DeLong's method [19]. The maximal Youden index was used to evaluate the cutoff point for discrimination, and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) as well as respective 95%CI were calculated for the prediction of consciousness recovery.

Statistical analysis was carried out on the SPSS version 20.0 software (SPSS, Chicago, IL, USA) except for the ROC curve analysis. A web-based free software (StAR: *http://melolab.org/star/home.php*) was used for the ROC curve analysis, and the AUCs from different variables were also compared [20]. A *P*-value less than 0.05 were considered to be statistically significant.

Results

In our study, 246 adult patients with ICH after surgical hematoma evacuation entered our ICU, and 55 patients were enrolled into our trial. Figure 1 shows our flowchart for this procedure. Nineteen patients (34.5%) recovered consciousness within 30 days after enrollment, including 4 patients on day 1, 9 patients on day 2 to day 10, 4 patients on day 11 to day 20, and 2 patients on day 21 to day 30. No patients died in the recovery group. In the consciousness nonrecovery group (n=36, 65.5%), 14 patients died, including 10 patients within 10 days after enrollment, 3 patients on day 11 to day 20, and 1 patient on day 21 to day 30. Among the patients who died, 3 patients' surrogates decided to withdraw support on day 8, day 16, and day 22 after enrollment.

Table 1 shows the information of patients at the study entry. Compared to the consciousness nonrecovery group, the APACHE II score was lower (*P*=0.040), and GCS was higher (*P*<0.001) in the recovery group than in the nonrecovery group, respectively. The patients' demographic characteristics did not present any significant differences, including ICH score, history, site and size of hematoma, type of surgical procedure, time of surgery, and time from the end of surgery to enrollment into our study.

The BIS values increased significantly after stimulation in the GCS-M assessment (68 [57–80] versus 64 [55–72], *P*<0.001). There is a significant correlation between the peak BIS after stimulation and the GCS-M, respectively (Spearman's *r*=0.590,
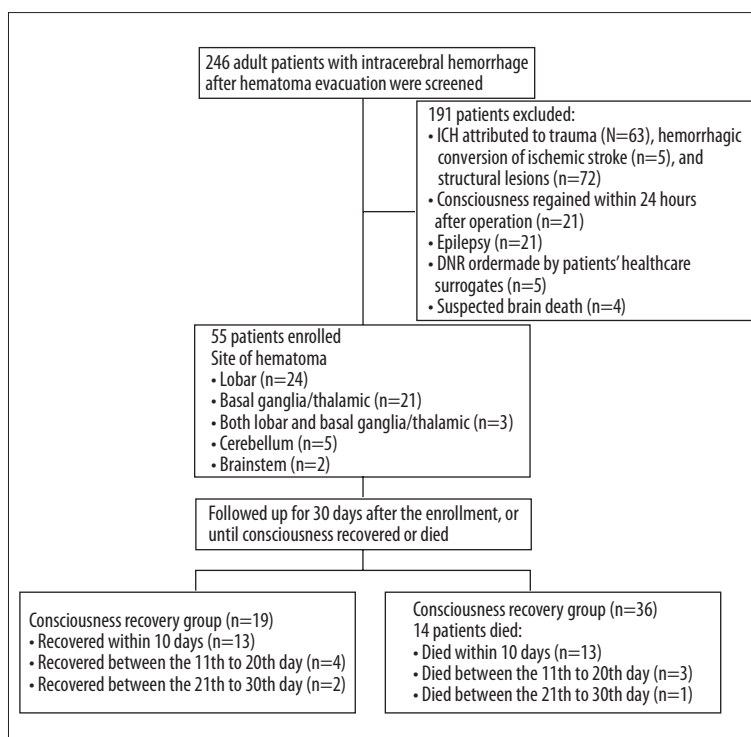
Figure 1. Patients flow chart.

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Table 1. Data collected at the study entry.

	Recovery group (n=19)		Nonrecovery group (n=36)		p
Age (years)	57	(47–66)	66	(55–73)	0.113
Male	10	(53%)	21	(58%)	0.685
APACHE II	15	(13–19)	18	(16–22)	0.040
GCS	8	(7–8)	6	(4–6)	<0.001
ICH score	3	(2–3)	3	(2–3)	0.369
History of hypertension	12	(63%)	26	(72%)	0.489
Antihypertensive drugs	11	(58%)	23	(64%)	0.663
Anticoagulation drugs	1	(5%)	4	(11%)	0.473
Site of hematoma					0.572
Lobar	9	(47%)	15	(42%)	
Basal ganglia/thalamic	8	(42%)	13	(36%)	
Both lobar and basal ganglia/thalamic	0		3	(8%)	
Cerebellum	2	(11%)	3	(8%)	
Brainstem	0		2	(6%)	
IVH	8	(42%)	13	(36%)	0.663
Hematoma volume (ml)	45	(27–57)	44	(29–60)	0.894
Type of surgery					0.953
Craniotomy	7	(37%)	16	(44%)	
Burrhole	4	(21%)	7	(19%)	
Craniotomy + EVD	7	(37%)	11	(31%)	
Burrhole + EVD	1	(5%)	2	(6%)	
Re-operation	2	(11%)	3	(8%)	0.788
Time from ictus to surgery (h)	26	(22–33)	29	(20–36)	0.257
Time from end of operation to enrollment (h)	17	(15–18)	17	(14–18)	0.759
Use of propofol for agitation	**1**	**(5.3%)**	**2**	**(5.6%)**	**>0.999**

Data are shown as n (%), mean ± standard deviation, or median (interquartile range). APACHE II – Acute Physiology and Chronic Health Evaluation II score; ICH – intracerebral hemorrhage; GCS – Glasgow Coma Scale; IVH – intra-ventricular hemorrhage; EVD – external ventricular drainage.

$P<0.001$). The peak BIS and the GCS-M in the consciousness recovery group increased significantly than in the nonrecovery group ($P<0.001$ for BIS and $P=0.001$ for GCS-M, Figure 2).

The AUCs of the BIS and the GCS-M were significantly different from 0.5, whereas the ICH scores were not (Table 2). For pairwise comparisons, the AUC of the BIS was higher than the GCS-M, significantly. The best cutoff points of BIS and GCS-M were 79 and 4, significantly. The sensitivity, specificity, PPV, and NPV are also shown in Table 2.

Discussion

In the present study, BIS monitoring was used on the first postoperative day in patients with ICH after surgical hematoma evacuation. Our main findings indicated that BIS values were elevated significantly in those patients with consciousness recovery than those without consciousness recovery 30 days post operation. The BIS had a higher predictive probability than traditional clinical measurements, such as the GCS-M and the ICH scores, for early consciousness recovery in patients with ICH.
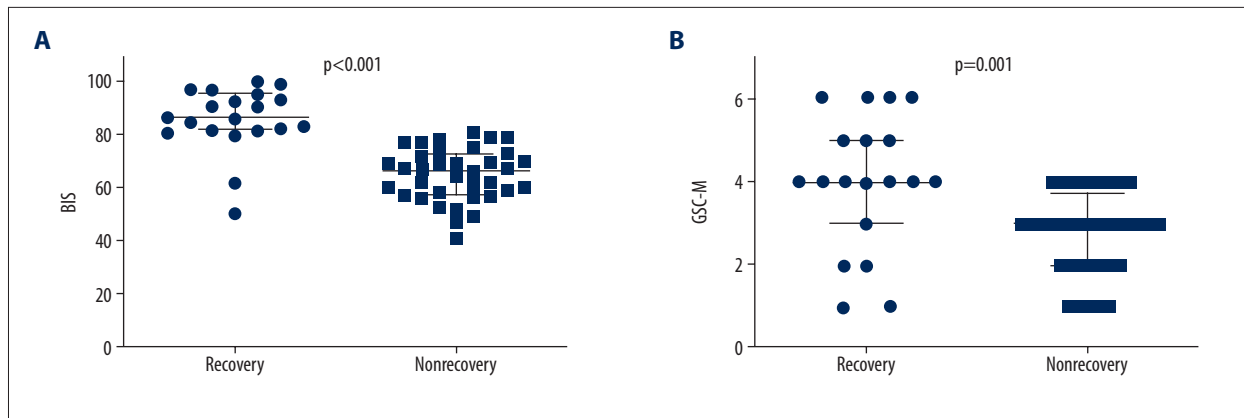
Figure 2. (**A, B**) Bispectral index (BIS) and Glasgow Coma Scale (GCS) in the consciousness recovery and nonrecovery group. Individual data, the median and interquartile range, and *P* value are as shown. The peak BIS and GCS-M of the consciousness recovery group were higher than that of the nonrecovery group, significantly.

Table 2. Data of ROC analysis.

	AUC (95% CI)	*p**	Best cutoff point	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
BIS **	0.97 (0.91–1.00)	<0.001	79	0.95 (0.72–1.00)	0.97 (0.84–1.00)	0.95 (0.72–1.00)	0.97 (0.84–1.00)
GCS-M	0.75 (0.59–0.91)	0.002	4	0.74 (0.49–0.90)	0.75 (0.57–0.87)	0.61 (0.39–0.80)	0.84 (0.66–0.94)
ICH score	0.57 (0.41–0.73)	0.396	–	–	–	–	–

* *p* value for the test of whether AUC was significantly different from 0.5; ** AUC was significantly higher than GCS-M, APACHE II and ICH score. ROC – receiver operating characteristic curve analysis; AUC – area under the curve; CI – confidence interval; BIS – the peak BIS value after GCS-M stimulation; GCS-M – motor responses to external stimuli in Glasgow Coma Scale; APACHE II – Acute Physiology and Chronic Health Evaluation II score; ICH – intracerebral hemorrhage.

The 30-day mortality in our study population (25.5%) was comparable to published data from population-based studies [2,21]. In the International Surgical Trial in Intracerebral Hemorrhage (STICH) study, the effects of early surgery were investigated in patients with spontaneous supratentorial ICH [22]. In the early surgery group, the mortality rates at 1 month and 6 months were 23% and 36%, respectively. In the STICH II study, only patients with lobar ICH were enrolled, and the mortality rates at 1 month and 6 months were 10% and 18%, respectively [23].

Factors associated with early deterioration and long-term outcome of spontaneous ICH have been systematically reviewed recently [4]. Typically, predictors of poor outcome included increasing age, decreasing GCS and ICH severity, such as ICH volume and distribution. To date, no studies have been performed to clarify the factors associated with early consciousness recovery in patients with ICH after surgical hematoma evacuation. Table 1 shows the baseline characteristics of those enrolled patients. Compared with the nonrecovery group, the APACHE II score of the recovery group was significantly lower and the GCS was significantly higher. In addition, GCS-M during the 12-hour period after enrollment was significantly higher in

the recovery group than in the nonrecovery group (Figure 2B). These results suggested that the overall severity of diseases (indicated by the APACHE II score) and the initial status of consciousness (indicated by the GCS-M evaluation) were associated with early recovery of consciousness.

A physical examination is the most widely used method for assessing the consciousness of patients with brain injuries. However, its application may be limited by the experiences of physicians, subjective errors and discontinuity [13]. An objective method of consciousness analysis is desirable. As a quantitative electroencephalography monitoring instrument, the BIS was initially developed to evaluate the depth of general anesthesia [24]. Through further research, the BIS is considered to be an indicator of neurological status. Our previous study [18] found that external stimuli resulted in increased BIS values in sedated patients, as reported by other investigators [25–27]. By using the cerebral state index (CSI), a quantitative electroencephalography monitoring instrument similar to the BIS, we also found that external stimuli increased CSI values in non-sedated patients with brain injury [28] and in postoperative patients with craniotomy [29]. In the present

study, BIS values increased significantly after external stimulation during the GCS-M assessment and correlated directly with the GCS-M. A standard subjective consciousness assessment incorporates the use of verbal and physical stimuli and observing the responses of the patient [13]. Similarly, BIS values collected after external stimulation should be more valid than those collected randomly. Therefore, we use the peak-stimulated BIS values for further predictive analysis of consciousness recovery.

Several studies have used BIS to predict the prognosis of patients with brain injury [6–9]. The results of studies of patients after cardiac arrest indicate that the BIS is an accurate and early predictor of long-term neurological outcomes [7–9]. Fabregas et al. enrolled comatose patients with brain trauma and subarachnoid hemorrhage (SAH) and found that the BIS had a high predictive probability for consciousness recovery [6]. In the present study, the enrolled patients were monitored by the BIS during the postoperative period and followed up to 30 days. Based on the consciousness status, the patients were assigned into consciousness recovery and nonrecovery groups. During the 12-hour BIS monitoring, the peak BIS values in the consciousness recovery group were significantly higher than those in the nonrecovery group after external stimulation and GCS-M (Figure 2). The AUCs of the BIS and the GCS-M showed a significant predictive probability of consciousness recovery, whereas the ICH score did not (Table 2). Moreover, the AUC of the BIS was significantly higher than that of the GCS-M. Not consistent with the previous reports [4], we did not find the predictive value of ICH score in this study. However, in our cohort, we recruited patients only after surgical hematoma evacuation. The average age was relatively young (median age of 57 and 66 years in the recovery and nonrecovery group) and the hematoma volume was relatively large (median volume of 45 and 44 mL in the recovery and nonrecovery group) (Table 1). This might be the reason why the ROC analysis of the ICH score was found to be non-significant in the present study. Our results suggest that BIS has a better predictive probability than GCS-M for short-term consciousness recovery in patients with ICH. BIS monitoring might be a good objective tool to assist in decision making for healthcare providers and families.

During the study, several measures were taken to guarantee the quality of the research. First, we recruited patients on the first postoperative day (with a median time of 17 hours from the end of the procedure to enrollment) to avoid the influence of anesthesia on BIS monitoring. Second, during the 12-hour monitoring window, the BIS and GCS-M measurements were repeated 4 times per patient to avoid bias caused by a single observation. Third, the GCS-M evaluator was blinded to the BIS monitor, while the investigators who analyzed the offline BIS data were blinded to the results of the consciousness assessment. Fourth, in the present study, the outcome of consciousness recovery was the focus and the GCS-M was selected as an indicator to assess the evaluation of consciousness [13]. Finally, we did not deliberately change the local routine practice. The outcomes of our study population are comparable to those reported in published data. Therefore, our results reflect the real clinical scenario.

However, our study had its limitations. First, we recruited spontaneous ICH patients after hematoma evacuation because the DNR decision is unlikely to be made in this population. Therefore, our results might not be applicable to patients who do not undergo surgery. Second, we only conducted short-term BIS monitoring during the acute phase. Long-term dynamic BIS monitoring contributes to a comprehensive representation of the changes in neurological function and progression of brain injury. Third, our results only reflected short-term outcomes without a follow up of more than 30 days after enrollment. Fourth, the current study is a single center trial, which was conducted in our hospital only, with a relatively small sample size. The results need to be confirmed with further investigations in a larger population.

Conclusions

The current study demonstrates that BIS might be a potential predictor for the consciousness recovery in spontaneous ICH patients undergone hematoma evacuation. Compared with those patients who did not regain consciousness, the BIS values were significantly higher in patients with consciousness recovery 30 days after surgery. In terms of early consciousness recovery in this population, the BIS value after external stimulation has a higher prediction probability than the traditional GCS-M and ICH score.

Conflict of interest

None.

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