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ORIGINAL RESEARCH

The Impact of Bispectral Index Monitoring on Outcomes in Spinal Cord Stimulation for Chronic Disorders of Consciousness

Xuanling Chen[1,*], Xuewei Qin[1,*], Yutong Zhuang[2], Zhengqian Li[3], Zhenhu Liang[4], Hua Zhang[5], Lan Yao[1], Xiaoli Li[6], Jianghong He[7], Xiangyang Guo[3]

[1]Department of Anesthesiology, Peking University International Hospital, Beijing, People's Republic of China; [2]Department of Neurosurgery, The Second School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, People's Republic of China; [3]Department of Anesthesiology, Peking University Third Hospital, Beijing, People's Republic of China; [4]Institute of Electrical Engineering, Yanshan University, Qinhuangdao, People's Republic of China; [5]Clinical Epidemiology Research Center, Peking University Third Hospital, Beijing, People's Republic of China; [6]The State Key Laboratory of Cognitive Neuroscience and Learning & IDG/McGovern Institute for Brain Research, Beijing Normal University, Beijing, People's Republic of China; [7]Department of Neurosurgery, Tiantan Hospital, Capital Medical University, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiangyang Guo, Peking University, Third Hospital, 49 huayuan North Road, Haidian District, Beijing, 100191, People's Republic of China, Email puthmzk@hsc.pku.edu.cn; Jianghong He, Beijing Tiantan Hospital, 119 South Fourth Ring Road West, Fengtai District, Beijing, 100069, People's Republic of China, Email hejianghong@sina.cn

Objective: To observe whether maintaining the appropriate depth of anesthesia with Bispectral Index (BIS) can improve the prognosis of Spinal Cord stimulation (SCS) implantation in patients with chronic Disorders of consciousness (DoC).

Methods: 103 patients with DoC undergoing SCS implantation were reviewed, and 83 patients with DoC were included according to the standard of inclusion and exclusion Criteria. Patients were divided into a BIS group (n =45) and a non-BIS group (n =38) according to whether BIS monitoring was used during the operation. The depth of anesthesia in the BIS group was maintained between 40–60. The anesthesiologist adjusted the depth of anesthesia in the non-BIS group according to clinical experience. Relevant information such as disease course, cause, anesthesia time, and operation time were collected. Preoperative CRS-$R_{(preoperative)}$ score, postoperative CRS-$R_{(24h)}$, and postoperative CRS-$R_{(3m)}$ changes were collected.

Results: The CRS-R(3m) score in the BIS group was higher than that in the non-BIS group $_{(preoperative)}$, and the difference was statistically significant ($P < 0.05$). In CRS-R $_{(24h)}$, the BIS group was higher than the non-BIS group, and the difference was statistically significant (X^2=8.787, P =0.004). The improvement of consciousness was included in the multivariate Logistic regression analysis model, and it was found that the thalamus was an independent factor affecting the improvement of consciousness ($P < 0.05$). During follow-up, 1 patient in the BIS group had a decrease in consciousness from MCS^- to VS/ UWS and 2 patients in the non-BIS group died during follow-up.

Conclusion: Patients can be benefit in hearing in CRS-R $_{(24h)}$. We recommend the use of BIS to monitor the depth of anesthesia in patients with DoC to improve patient outcomes.

Keywords: chronic disturbance of consciousness, vegetative state/unresponsive wakefulness syndrome, spinal cord stimulation, general anesthesia, bispectral index, improved coma recovery scale

With the rapid development of surgical technology, the enhancement of intensive care rescue ability, and the popularization of cardiopulmonary resuscitation technology, the number of craniocerebral injury patients surviving after all-out treatment has increased significantly. DoC refers to various states of loss of consciousness caused by severe brain injuries, such as coma, Vegetative state (VS)/ Unresponsive Wakefulness Syndrome (UWS) and Minimally conscious state (MCS).[1–3] VS/UWS refers to a state in which the basic reflexes of the brain stem and the sleep-wake cycle are preserved,[4] with spontaneous eye opening or stimulated eye-opening, but with unconscious content.[3,5] In contrast to VS/

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UWS, MCS can exhibit residual sensory and partial conscious retention,[6–8] such as pain localization, visual object tracking,[6] or target gaze,[9] but cannot complete compliance activities. The mutual change of the two states also represents a change in the level of consciousness. At present, the gold standard for clinical evaluation of DoC is the Coma Recovery Scale-Revised (CRS-R),[10–12] which includes six aspects of auditory, visual, motor, promotor/verbal function, communication, and arousal level. Due to its reliability, it is currently recommended by the mainstream, especially in the identification of VS/ UWS and MCS.[13]

In treating patients with DoC, the medical community utilizes a variety of approaches, categorized as non-invasive, invasive, and mechanical therapies. Non-invasive treatments include the use of medications to modulate neurotransmitters and electromagnetic stimulation techniques such as oxygen therapy,[14,15] music therapy,[15–17] stem cell therapy,[18,19] amantadine,[20,21] etc., have little therapeutic effect.[1,22] Invasive treatments focus on deep brain stimulation (DBS),[23] SCS, cortical electrical stimulation,[24] vagus nerve electrical stimulation,[25,26] etc. SCS is currently the recommended treatment method.[27–29] SCS represents a promising neuromodulation technique for the treatment of patients with DoC. In SCS, electrodes are implanted into the epidural space at C2–C4, delivering electrical impulses to stimulate the ascending reticular activating system and regulate the awareness circuit.[28] Studies have shown that SCS can directly activate the reticular structure and stimulate the thalamus,[30,31] or increase the cerebral blood flow in the injured area through the brain stem pathway, improve the levels of neurotransmitters and neuromodulators, and promote the neuroplasticity of the central nervous system.[32] Mechanical therapies involve transcranial-focused ultrasound (FUS), which utilizes ultrasound waves to penetrate the skull and affect brain activity.

At present, the depth of sedation under general anesthesia is usually measured by BIS in clinical practice. BIS is a medical technology utilized to monitor the depth of anesthesia by analyzing electroencephalogram (EEG) signals to assess a patient's response to hypnotic agents. The BIS monitor integrates multiple EEG descriptors into a single, dimensionless value that ranges from 0 to 100, where 0 denotes the resting state of the EEG (inactive) and 100 indicates a fully awake state. The BIS calculation is based on the statistical processing of the EEG signal, which combines the frequency and power spectra of the EEG, the amount of burst suppression, and the degree of EEG synchronization. As the degree of sedation increases, the in-phase coupling within the frequency of the signal increases, and the extent of this coupling represents a coherent pattern. As the amount of hypnotic drug is increased, distinctive changes in biphasic coherence patterns occur, and these patterns serve as markers of the level of sedation. Maintaining BIS within the range of 40–60 in perioperative period is considered to be a more appropriate depth of anesthesia.[33] Too deep or too shallow anesthesia will increase perioperative mortality and intraoperative awareness.[34,35] Is BIS monitoring helpful for the treatment of DoC patients undergoing SCS implantation under general anesthesia? There are no relevant studies. The purpose of this study was to investigate the effect of BIS monitoring in the perioperative period on the outcome of resuscitation therapy in patients with DoC.

Methods

General Information

103 patients with DoC admitted to the Department of Neurosurgery of Peking University International Hospital were collected from 2019.01 to 2021.12. The patient data was collected from the inpatient information system and anesthesia information system (approved by the Ethics Committee of Peking University International Hospital, Ethics number: 2022-KY-0023-01; International registration code: ChiCTR2300069756). Inclusion criteria: ① Age 18–65 years old; ②No central sedative drugs were used 24 hours before anesthesia; ③ No prior history of brain tumor or family psychosis; ④ Tracheotomy. ⑤Frontal lobe was intact. Exclusion criteria: ① single/multiple organ failure; ② Severe coagulation dysfunction; ③ the circulatory system is not stable; ④metal implants in the brain⑤ Lost follow-up. A total of 83 patients were included in the study, divided into the BIS group (n =45) and the non-BIS group (n =38) according to whether BIS was monitored in the perioperative period. The general data of the two groups are shown in Figure 1. and Table 1.

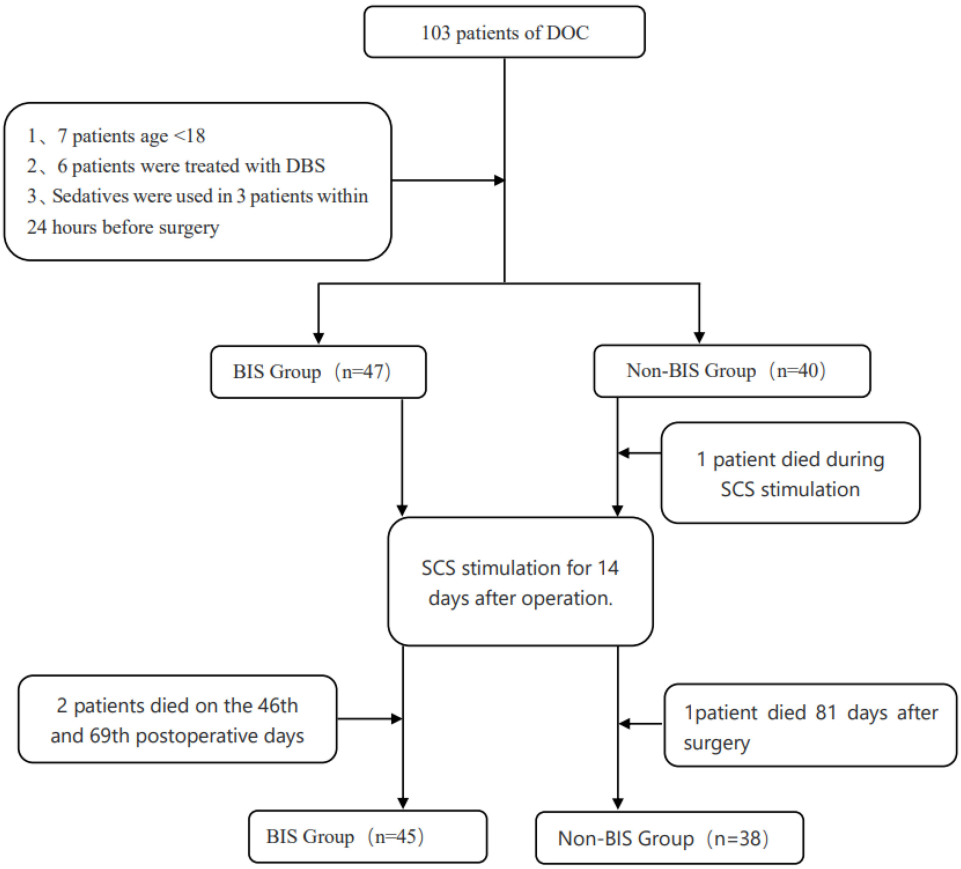


Figure 1 Flow Chart.

Methods and Monitoring of Anesthesia

ECG, pulse oxygen saturation (SPO_2), invasive arterial blood pressure, end-tidal carbon dioxide ($EtCO_2$), body temperature, and intermittent blood gas analysis. BIS (Covidien. (2014). BIS VISTA, Mansfield, U.S.A) Group: Clean the patient's facial skin to remove sweat and grease to ensure the conductivity of the electrode pads. Place the specialized BIS monitoring electrode pads on the patient's forehead, about 5 cm above the root of the nose, in the temple area (between the eye canthus and hairline), and directly above the eyebrow ridge parallel to it. After confirming the position of the electrode pads, press firmly for 5 seconds to enhance contact with the skin. Connect the monitoring device lead, and the routine monitoring interval is

Table 1 Demographic Characteristics of Patients in Both Groups

Event	BIS Group	Non-BIS Group	t /X^2	*P*
Gender				
Male	33(73.3%)	27(71.1%)	0.053	0.817
Female	12(26.7%)	11(28.9%)		
Age (years)	48.04±13.61	50.16±14.89	0.675	0.501
Height (cm)	170.33±7.09	170.60±6.56	0.180	0.858
Weight (kg)	63.50±15.28	57.10±12.19	−0.1035	0.314
Etiology				
TBI	21(46.7%)	17(44.7%)	0.031	0.860
CVA	24(53.3%)	21(55.3%)		
Duration of disease (month)	6(3,12)	6(4,7)	−0.648	0.517
Operation time (min)	149.40±75.45	147.05±57.93	−0.157	0.876
Duration of anesthesia (min)	206.69±110.38	181.62±114.79	−0.1005	0.318

15 seconds (BIS value between 40 and 60 is generally considered an appropriate anesthesia depth). The anesthesia machine is connected to the tracheotomy tube. Propofol 1mg/kg, Sufentanil 0.4μg/kg, and Rocuronium 0.8mg/kg were used for induction under general anesthesia. After induction, the ventilation mode was changed to mechanical ventilation, the respiratory rate was 10~12 times /min, the tidal volume was 8 ~ 10mL/kg, and $EtCO_2$ was maintained between 35 ~ 45mmHg. Anesthetic maintenance: Propofol 2 ~ 3mg/kg·h, Remifentanil 0.1 ~ 0.2ug/kg·min. The depth of anesthesia in the BIS group was maintained between 40–60, and the depth of anesthesia in the non-BIS group was adjusted by the anesthesiologist according to clinical experience. After the operation, the patient was given 200mg of Sugammadex sodium for antagonism. When the patient recovered from spontaneous breathing and inhaled air for more than 10 minutes, the SPO2 > 90% then was transferred to the rehabilitation department for further treatment.

Surgical Methods and CRS-R Scale Evaluation

SCS implantation surgery were performed by the same senior neurosurgeon. In the prone position, the T_6-T_7 space was identified by X-ray as the puncture point, and the puncture needle was inserted into the skin at an Angle of about 30 degrees. After the tip of the needle reached the epidural space, the stimulation electrode was delivered to the level of the C_2 vertebral body with the assistance of an X-ray, the electrical impedance of the electrode was tested, and the electrode lead was fixed after the puncture needle met the requirements. After the operation, the patients was transferred to the rehabilitation department of our hospital for awakening treatment and regular follow-up. All patients' CRS-R scores were performed by the same neurosurgeon (qualified for CRS-R assessment).

Data Collection and Analysis

Data was collected from the inpatient information system and anesthesia information system of Peking University International Hospital. Data such as gender, age, height, weight, etiology, course of disease, anesthesia time and operation time were collected. CRS-R $_{(preoperative)}$, CRS-R $_{(24h)}$, and CRS-R $_{(3m)}$ scores and improvements in consciousness were collected. Awareness improvement criteria: Patients classified as VS/ UWS at the start of the study had their awareness improvement rise to MCS^-, MCS^+, or EMCS; patients classified as MCS^- at the start of the study had their awareness improvement rise to MCS^+ or EMCS at the start of the study. If the clinical diagnosis at the end of treatment did not improve compared to the start of the study, the clinical outcome was classified as invalid, as shown in Table 2.

Table 2 CRS-R Rating Scale

Auditory		Visual		Motor		Oromotor/ Verbal Function		Communication		Arousal	
Consistent movement to command	4	Object recognition	5	Functional Object use	6	Intelligible verbalization	3	Functional: Accurate	2	Attention	3
Reproducible movement to command	3	Object localization: Reaching	4	Automatic motor response	5	Vocalization/Oral movement	2	Non-functional: Intentioanl	1	Eye opening w/o stimulation	2
Localization to sound	2	Pursuit eye movements	3	Object manipulation	4	Oral reflexive movement	1	None	0	Eye opening with stimulation	1
Auditory startle	1	Fixation	2	Localization to noxious stimulation	3	None	0			None	0
None	0	Visual Startle	1	Flexion withdrawal	2						
		None	0	Abnormal posturing	1						
				None	0						

Notes: VS/ UWS | MCS | EMCS.

Statistical Processing

SPSS 26.0 statistical software was used for data analysis. The measurement data conforming to normal distribution were expressed as mean ± standard or median (Interquartile Range). Paired *T*-test or Wilcoxon test was performed. The count data were presented as [example (%)]. Fisher test and Mann–Whitney *U*-test were used to compare the differences between groups. Multivariate Logistic regression analysis was used, and the improvement of consciousness was included in the multivariate Logistic regression analysis model as the dependent variable. Anesthetic duration time, Propofol, and Remifentanil were included. CRS-R score at three moments: $CRS\text{-}R_{(preoperative)}$, $CRS\text{-}R_{(24h)}$, $CRS\text{-}R_{(3m)}$; Disease event: cause, course of disease and damaged brain area: temporal lobe, parietal lobe, frontal lobe, basal ganglia, thalamus, brainstem, occipital lobe and pontine as independent variables. $P < 0.05$ was statistically significant.

Results

Comparison of general data between the two groups showed no statistical significance ($P > 0.05$), as shown in Table 1.

There was no statistical significance in the composition ratio of consciousness level during preoperative, 24h after surgery and 3m after surgery between the two groups ($P > 0.05$); The $CRS\text{-}R_{(3m)}$ of the BIS group was higher than that of the non-BIS group, and the difference was statistically significant ($P < 0.05$). The improvement of consciousness level 3 months after surgery was better than a preoperative period, and the difference was statistically significant ($P < 0.05$). The score of $CRS\text{-}R_{(3m)}$ was higher than that of $CRS\text{-}R_{(preoperative)}$, and the difference was statistically significant ($P < 0.05$). There was no significant difference between $CRS\text{-}R_{(24h)}$ and $CRS\text{-}R_{(preoperative)}$ ($P > 0.05$). See Table 3.

Before surgery, there was no statistical significance in CRS-R score in 6 aspects between the two groups ($P > 0.05$); 24h after surgery, the auditory CRS-R score of the BIS group was higher than that of the non-BIS group, the difference was statistically significant ($P < 0.05$), and the other aspects were not statistically significant ($P > 0.05$). 3 months after surgery, there was no statistical significance in CRS-R score in 6 aspects between the two groups ($P > 0.05$), (Figure 2 A-C)

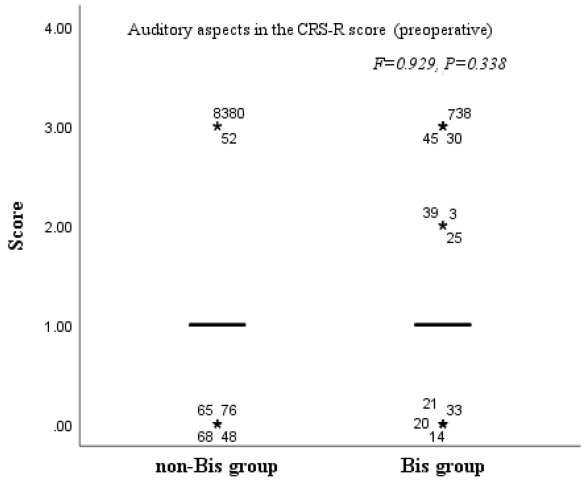
Logistic regression analysis of consciousness improvement and multiple factors during operation

Events related to anesthesia: duration of anesthesia, Propofol, Remifentanil; CRS-R score at three moments: $CRS\text{-}R_{(preoperative)}$, $CRS\text{-}R_{(24h)}$, $CRS\text{-}R_{(3m)}$; Events of the disease itself: cause of disease, course of disease and damaged brain area: The temporal lobe, parietal lobe, frontal lobe, basal ganglia, thalamus, brainstem, occipital lobe and Pontus were taken as independent variables, and the improvement of consciousness as dependent variables were included in the multivariate Logistic regression analysis model. Through regression analysis, the thalamus was considered to be an

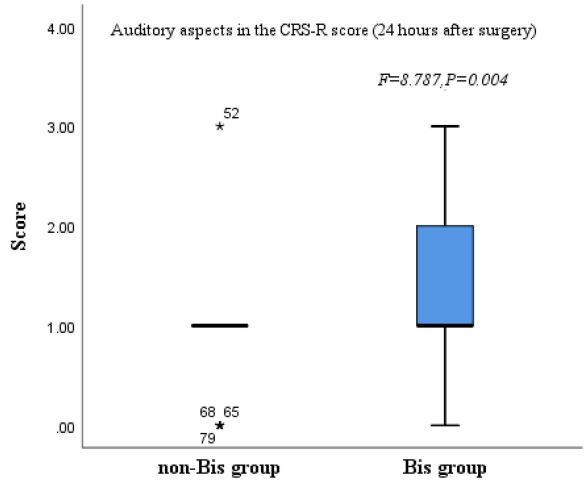
Table 3 Comparison of Preoperative Diagnosis, Outcome, and CRS-R Score Between the Two Groups

Parameters	BIS (*n*=45)	Non-BIS (*n*=38)	*P*
Preoperative diagnosis			0.223
VS/UWS	23 (51.1%)	26 (68.4%)	
MCS-	16 (35.6%)	10 (26.3%)	
MCS+	6 (13.3%)	2 (5.3%)	
CRS-R (Preoperative)	7.60 ± 2.59	7.55 ± 2.50	0.933
Postoperative diagnosis (24h)			
VS/UWS	23 (51.1%)	26 (68.4%)	
MCS-	16 (35.6%)	10 (26.3%)	
MCS+	6 (13.3%)	2 (5.3%)	
CRS-R (24h of Postoperative)	7.91 ± 4.07	7.55 ± 2.43	0.514
Postoperative diagnosis (3m)			
VS/UWS	5 (11.1%)	3 (7.9%)	0.872
MCS-	11 (24.4%)	8 (21.1%)	
MCS+	11 (24.4%)	12 (31.6%)	
EMCS	18 (40.0%)	15 (39.5%)	
CRS-R (3m of Postoperative)	11.29 ± 4.15*	9.13 ± 4.07*	0.020

Notes: *Within groups, *P*<0.05.



A



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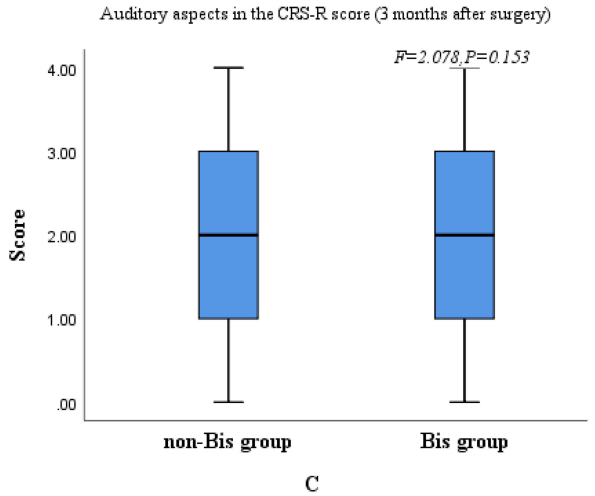

C

Figure 2 Comparison of auditory in CRS-R before surgery (**A**), 24h after surgery (**B**), and 3 months after surgery (**C**). As shown in Fig A, there was no statistically significant difference between the two groups in preoperative auditory scores (X^2=0.929, *P* =0.338). Fig B, the auditory score of the two groups 24 hours after surgery was compared. The auditory score of the BIS group was higher than that of the non-BIS group, and the difference was statistically significant (X^2=8.787, *P* =0.004). The comparison of hearing scores 3 months after surgery between the two groups showed no statistical significance (X^2=2.078, *P* =0.153).

Table 4 Multivariate Logistic Regression Analysis of Consciousness Improvement

		B	Sig	t	OR [95CI]
Anesthesia-related events	Duration of anesthesia	0.002	0.994	0.008	1[1, 1.01]
	Propofol	0.434	0.743	0.328	1.54[0.12, 20.49]
	Remifentanil	−13.386	0.993	−0.009	0[0, inf]
CRS-R	$CRS\text{-}R_{(preoperative)}$	0.466	0.005	2.781	1.59[1.15, 2.21]
	$CRS\text{-}R_{(24h)}$	−0.420	0.538	−0.617	0.66[0.17, 2.5]
	$CRS\text{-}R_{(3m)}$	−0.208	0.105	−1.622	0.81[0.63, 1.04]
Events of the disease itself	Cause	−0.641	0.345	−0.943	0.53[0.14, 2]
	Course	−0.08	0.155	−1.422	0.92[0.83, 1.03]
Damaged brain area	Temporal lobe	−1.255	0.195	−1.295	0.29[0.04, 1.9]
	Parietal lobe	1.935	0.070	1.812	6.92[0.85, 56.07]
	Frontal lobe	−0.399	0.662	−0.437	0.67[0.11, 4.02]
	Basal ganglia	−0.066	0.932	−0.086	0.94[0.21, 4.23]
	Thalamus	−2.855	0.039	−2.066	0.06[0, 0.86]
	Brainstem	−1.462	0.117	−1.568	0.23[0.04, 1.44]
	Occipital lobe	2.1	0.073	2.925	445.78[3.49, 26,548.57]
	Pontus	−2.555	0.173	−1.364	0.08[0,3.06]

independent influencing factor for the improvement of consciousness, while the other independent variables were not high-risk factors for the improvement of consciousness ($P > 0.05$), as shown in Table 4.

Adverse Outcome

In 83 patients with DoC, we followed up to 3 months after operation. The consciousness of 1 patient in the BIS group decreased from the original MCS^- to VS/ UWS; In the BIS group, 2 patients died on the 46th and 69th postoperative days.In the non-BIS group, 2 patients died during SCS stimulation and on the 81st day after surgery, respectively. The causes of death were pulmonary infection and systemic multiple organ failure.

Discussion

It is very difficult for current medical technology to improve the consciousness of DoC patients, and studies have pointed out that SCS plays a certain role in improving the consciousness of DoC patients.[21] The SCS procedure entails the implantation of neurostimulation electrodes within the high cervical spinal canal of the patient, whereby pulsed electrical currents are applied to stimulate the spinal nerves. This stimulation increases cerebral blood flow and activates the ascending reticular activating system, thereby improving brain circulation, exciting the cerebral cortex, and promoting the patient's return to consciousness.[22] The surgical procedure is minimally invasive and does not damage any of the patient's neural tissues. The surgeon performs SCS with the patient in a prone position and braking, and general anesthesia is the only option. Whether general anesthesia drugs have an effect on the recovery of consciousness in patients with DoC, and whether the depth of anesthesia monitoring is helpful to the recovery of consciousness in such patients are the main purposes of this study (SCS).

By measuring the frequency and power of electroencephalogram and processing them with digital standard, the comprehensive monitoring index BIS of anesthesia depth was obtained. BIS is a relatively objective indicator to evaluate sedation level,[29] and it can evaluate cortical electrical inhibition or excitation[30] and guide anesthetic administration, which can reduce the occurrence of adverse reactions.[31] However, at present, BIS is mainly used for patients with unconscious disorders in clinical practice, and there are few relevant studies about whether BIS can accurately monitor the sedation depth of DoC patients. Xue et al[32] found that BIS could judge the cerebral ischemia and hypoxia status of patients with craniocerebral injury and assess the prognosis, and some experiments suggested that the use of BIS monitoring in general anesthesia of DoC patients might be useful for patients.[29,33] In this study, we found that there was no significant difference in the value of $CRS\text{-}R_{(24h)}$ compared with that before surgery, indicating that the short-term effect of anesthetic drugs had little impact on patients with DoC. Because BIS can be more accurate in monitoring the

depth of anesthesia, effectively control the state of anesthesia, avoid excessive sedation, and reduce the impact on brain function, it may help promote nerve remodeling and functional recovery of patients in the rehabilitation process. In this study, compared with the CRS-R $_{(3m)}$ score and CRS-R $_{(preoperative)}$ score, the score of the BIS group increased significantly, which was exactly in line with the role of BIS monitoring. However, the proper BIS value of patients with DoC under general anesthesia and its exact effect on the improvement of consciousness need to be verified by larger samples and increased long-term follow-up.

Hearing is the primary way to distinguish cognitive abilities in patients with DoC, such as UWS, MCS, or cognitive-motor dissociation (cognitive-motor dissociation).[35] Some studies have observed an increase in brain response after significant stimulation of DoC patients, especially in the auditory system, with significant improvements in brain sensitivity[36–38] and brain function.[12,13,39] The study of Boly et al[40,41] also proved that the auditory system is highly sensitive to changes at the level of consciousness. Heine et al[42] compared the activation of the auditory cortex with the conscious state of the patient in the clinic and proposed that the retention of the auditory cortex might be an indicator of the retention of consciousness. The above studies all indicate the correlation between hearing and consciousness. Propofol is a commonly used general anesthetic drug, and its mechanism of action is to inhibit the excitability of the central nervous system by enhancing the inhibitory effect of the neurotransmitter gamma-aminobutyrate (GABA).[34] If the sedation depth is too deep, propofol may excessively inhibit the activity of the nervous system, including the brain's ability to perceive and process external stimuli, including the auditory system. We found that the hearing score in the CRS-R $_{(24h)}$ rating scale in the BIS group was higher than that in the non-BIS group. The author believes that BIS monitoring can reduce the dosage of propofol and reduce its inhibition on the auditory system, which seems to have certain benefits for the short-term hearing and cognitive function improvement of DoC patients.

The thalamus and thalamic neural network are the relay stations for cortical nerve command delivery and upward transmission of sensory neurons,[43] and are part of the upwelling tegmental activation system of the midbrain, so the thalamic network system is a key structure for maintaining arousal.[44] In this study, it was found that the less thalamus involved in cranial injury, the better the awakening effect 3 months after surgery, indicating that the thalamus plays a key role in the neural correlation theory of consciousness from the perspective of neuroanatomy and functional neural brain network.[45–47] Dolce et al[48] found that thalamic injury was common in VS/UWS patients, and neuronal death in the thalamus was also the most common pathological outcome.[49] The relative preservation of corticothalamic connections in MCS patients may play an important role in supporting residual consciousness[50] and cognitive function.[19] Even in the most severe multifocal brain injuries associated with permanent VS/UWS, large-scale neural electrical activity has been demonstrated in the thalamic network system, which provides a physiological basis for arousal therapy in such patients.[51] Zhang et al[52] proposed that the functional connectivity between the thalamus and the whole brain could be used as an imaging marker to evaluate the prognosis of patients with DoC, as well as an indicator to evaluate the potential conscious function of the remaining brain network. Therefore, the less thalamus involved in craniocerebral injury, the better the effect of 3-month awakening therapy.

This study is retrospective. Whether BIS can truly reflect the anesthesia status of patients with DoC needs further investigation and confirmation. Keeping BIS between 40–60 is a more appropriate depth for surgical anesthesia for normal people, but for patients with DoC, the appropriate depth should be further explored. In the future, we will improve the clinical trial design and conduct prospective controlled studies with large samples and extended follow-up time to enhance the credibility of the research results.

There are some limitations to this paper. First, due to the retrospective research design, this somewhat limits our ability to make inferences about causality. Second, the sample size of the study was relatively small, which may affect the generalizability of the findings. In addition, the applicability of the BIS monitoring technique in a population of patients with DoC and the determination of the optimal depth of anesthesia needs to be further validated by additional studies. Furthermore, only a 3-month follow-up was conducted in this study, which limits our understanding of long-term effects. Finally, because the data came from only a single center, there may have been a selection bias, which may also have had some impact on the results of the study. Nonetheless, our study provides valuable preliminary findings and points the way for future research.

In conclusion, maintaining BIS between 40–60 during SCS implantation in patients with DoC may help increase the hearing score of patients 24 hours after awakening therapy.

Data Sharing Statement

The data and materials used and/or analyzed in the current study are available from the corresponding author upon reasonable request. Written informed consent was obtained from the individual(s) and/or the legal guardian/next of kin of minor(s) for the publication of any potentially identifiable images or data included in this article.

Ethics Approval and Consent to Participate

The study adhered to the principles outlined in the Declaration of Helsinki and obtained an exemption from informed consent.

Approval for the study was obtained from the institutional review committee of Peking University International Hospital (Approval No.: 2022-KY-0023-01).

Confidentiality Statement

This study is committed to maintaining the strictest standards of patient data confidentiality. All patient records will be accessed and reviewed in a secure environment, with access limited to study personnel who require it for research purposes. Data will be de-identified to remove all personal identifiers, ensuring that the information cannot be linked back to individual patients. Any data storage and transmission will adhere to the highest security protocols to prevent unauthorized access or disclosure. The findings of the study will be reported in an aggregate form that does not reveal any individual patient's information.

Registration

International registration code: ChiCTR2300069756.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing commercial or financial interests that could be considered a potential conflict of interest in conducting this study.

References

1. Eapen BC, Georgekutty J, Subbarao B, Bavishi S, Cifu DX. Disorders of Consciousness. *Phys Med Rehabil Clin N Am*. 2017;28(2):245–258. doi:10.1016/j.pmr.2016.12.003
2. Kondziella D, Bender A, Diserens K, et al. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. *Eur J Neurol*. 2020;27(5):741–756. doi:10.1111/ene.14151
3. Monti MM, Laureys S, Owen AM. The vegetative state. *BMJ*. 2010;341:c3765. doi:10.1136/bmj.c3765
4. Cavanna AE, Shah S, Eddy CM, Williams A, Rickards H. Consciousness: a neurological perspective. *Behav Neurol*. 2011;24(1):107–116. doi:10.3233/BEN-2011-0322

5. Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (2). *N Engl J Med*. 1994;330(22):1572–1579. doi:10.1056/NEJM199406023302206.
6. Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *J Neurol*. 2011;258(7):1373–1384. doi:10.1007/s00415-011-6114-x
7. Laureys S, Perrin F, Faymonville ME, et al. Cerebral processing in the minimally conscious state. *Neurology*. 2004;63(5):916–918. doi:10.1212/01.wnl.0000137421.30792.9b
8. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. *Lancet Neurol*. 2004;3(9):537–546. doi:10.1016/S1474-4422(04)00852-X
9. Prakash J, Ganiger VC. Acute Kidney Injury in Pregnancy-specific Disorders. *Indian J Nephrol*. 2017;27(4):258–270. doi:10.4103/0971-4065.202406
10. Rosenbaum AM, Giacino JT. Clinical management of the minimally conscious state. *Handb Clin Neurol*. 2015;127:395–410. doi:10.1016/B978-0-444-52892-6.00025-8
11. Bruno MA, Soddu A, Demertzi A, et al. Disorders of consciousness: moving from passive to resting state and active paradigms. *Cogn Neurosci*. 2010;1(3):193–203. doi:10.1080/17588928.2010.485677
12. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil*. 2004;85(12):2020–2029. doi:10.1016/j.apmr.2004.02.033
13. Rüegg S, Sutter R. All in the numbers? Computational prediction of optimal anaesthetic weaning in status epilepticus. *Brain*. 2020;143(4):1048–1050. doi:10.1093/brain/awaa073
14. Xie K, Wang P. Clinical study on effect of HBO plus electric stimulation on treatment for the vegetative state. *Acta Neurochir Suppl*. 2003;87:19–21. doi:10.1007/978-3-7091-6081-7_5
15. O'Kelly J, James L, Palaniappan R, Taborin J, Fachner J, Magee WL. Neurophysiological and behavioral responses to music therapy in vegetative and minimally conscious States. *Front Hum Neurosci*. 2013;7:884. doi:10.3389/fnhum.2013.00884
16. Okumura Y, Asano Y, Takenaka S, et al. Brain activation by music in patients in a vegetative or minimally conscious state following diffuse brain injury. *Brain Inj*. 2014;28(7):944–950. doi:10.3109/02699052.2014.888477
17. Lancioni GE, Singh NN, O'Reilly MF, Sigafoos J, Desideri L. Music Stimulation for People with Disorders of Consciousness: a Scoping Review. *Brain Sci*. 2021;11(7):858. doi:10.3390/brainsci11070858
18. Hazell AS. The Vegetative State and Stem Cells: therapeutic Considerations. *Front Neurol*. 2016;7:118. doi:10.3389/fneur.2016.00118
19. Liem NT, Chinh VD, Phuong DTM, et al. Outcomes of Bone Marrow-Derived Mononuclear Cell Transplantation for Patients in Persistent Vegetative State After Drowning: report of Five Cases. *Front Pediatr*. 2020;8:564. doi:10.3389/fped.2020.00564
20. Gao Y, Zhang Y, Li Z, Ma L, Yang J. Persistent vegetative state after severe cerebral hemorrhage treated with amantadine: a retrospective controlled study. *Medicine*. 2020;99(33):e21822. doi:10.1097/MD.0000000000021822
21. Gao Y, Ma L, Liang F, et al. The use of amantadine in patients with unresponsive wakefulness syndrome after severe cerebral hemorrhage. *Brain Inj*. 2020;34(8):1084–1088. doi:10.1080/02699052.2020.1780315
22. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. *Nat Rev Neurol*. 2014;10(2):99–114. doi:10.1038/nrneurol.2013.279
23. Mattogno PP, Barbagallo G, Iacopino G, et al. Recovery from Chronic Diseases of Consciousness: state of the Art in Neuromodulation for Persistent Vegetative State and Minimally Conscious State. *Acta Neurochir Suppl*. 2017;124:19–25. doi:10.1007/978-3-319-39546-3_4
24. Xie Y, Zhang T. Repetitive transcranial magnetic stimulation improves consciousness disturbance in stroke patients: a quantitative electroencephalography spectral power analysis. *Neural Regen Res*. 2012;7(31):2465–2472. doi:10.3969/j.issn.1673-5374.2012.31.008
25. Yifei W, Yi Y, Yu W, et al. Transcutaneous auricular vague nerve stimulation improved brain connection activity on patients of disorders of consciousness: a pilot study. *J Tradit Chin Med*. 2022;42(3):463–471. doi:10.19852/j.cnki.jtcm.2022.03.012
26. Edlow BL, Sanz LRD, Polizzotto L, et al. Therapies to Restore Consciousness in Patients with Severe Brain Injuries: a Gap Analysis and Future Directions. *Neurocrit Care*. 2021;35(Suppl 1):68–85. doi:10.1007/s12028-021-01227-y
27. Wang Y, Bai Y, Xia X, Yang Y, He J, Li X. Spinal cord stimulation modulates complexity of neural activities in patients with disorders of consciousness. *Int J Neurosci*. 2020;130(7):662–670. doi:10.1080/00207454.2019.1702543
28. Yamamoto T, Katayama Y, Obuchi T, Kobayashi K, Oshima H, Fukaya C. Deep brain stimulation and spinal cord stimulation for vegetative state and minimally conscious state. *World Neurosurg*. 2013;80(3–4):S30.e1–S30.e9. doi:10.1016/j.wneu.2012.04.010
29. Zhuang Y, Kai-tian CHEN, Yang Y, et al. Application of neuroelectrophysiological monitoring technology in prolonged disorders of consciousness. *Chin J Contemp Neurol Neurosurg*. 2020;20(11):936–943. doi:10.3969/j.issn.1672-6731.2020.11.002
30. Yamamoto T, Katayama Y, Obuchi T, Kobayashi K, Oshima H, Fukaya C. Spinal cord stimulation for treatment of patients in the minimally conscious state. *Neurol Med Chi*. 2012;52(7):475–481. doi:10.2176/nmc.52.475
31. Visocchi M, Tartaglione T, Romani R, Meglio M. Spinal cord stimulation prevents the effects of combined experimental ischemic and traumatic brain injury An MR study. *Stereotact Funct Neurosurg*. 2001;76(3–4):276–281. doi:10.1159/000066731
32. Lammi MH, Smith VH, Tate RL, Taylor CM. The minimally conscious state and recovery potential: a follow-up study 2 to 5 years after traumatic brain injury. *Arch Phys Med Rehabil*. 2005;86(4):746–754. doi:10.1016/j.apmr.2004.11.004
33. Lim HK, Jung WS, Aizenstein HJ. Aberrant topographical organization in gray matter structural network in late life depression: a graph theoretical analysis. *Int Psychogeriatr*. 2013;25(12):1929–1940. doi:10.1017/S104161021300149X
34. Mahmood S, El-Menyar A, Shabana A, et al. Bispectral index as a predictor of unsalvageable traumatic brain injury. *Brain Inj*. 2017;31(10):1382–1386. doi:10.1080/02699052.2017.1330966
35. Qian LI, Wei MA. Correlation between electroencephalogram monitoring of perioperative anesthesia depth and prognosis of patients. *J Southwest Med Univ*. 2023;46(02):93–97. doi:10.3969/j.issn.2096-3351.2023.02.001
36. Schnakers C, Ledoux D, Majerus S, et al. Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders. *Brain Inj*. 2008;22(12):926–931. doi:10.1080/02699050802530565
37. Avidan MS, Zhang L, Burnside BA, et al. Anesthesia awareness and the bispectral index. *N Engl J Med*. 2008;358(11):1097–1108. doi:10.1056/NEJMoa0707361

38. Wang D, Song Z, Zhang C, Chen P. Bispectral index monitoring of the clinical effects of propofol closed-loop target-controlled infusion: systematic review and meta-analysis of randomized controlled trials. *Medicine*. 2021;100(4):e23930. doi:10.1097/MD.0000000000023930
39. Xin XUE, Ruihao LI. REN Haijun.Application and progress of bispectral index monitoring technology in neurosurgery. *Chin J Neurosurg Dis Res*. 2018;17(06):570–572.
40. Wang XF, Wang Q, Bai XM, et al. Research progress of bispectral index in evaluating severity and prognosis of brain injury. *J Clin Neurosurg*. 2021;18(06):714–716+720. doi:10.3969/j.issn.1672-7770.2021.06.025
41. Heine L, Corneyllie A, Gobert F, Luauté J, Lavandier M, Perrin F. Virtually spatialized sounds enhance auditory processing in healthy participants and patients with a disorder of consciousness. *Sci Rep*. 2021;11(1):13702. doi:10.1038/s41598-021-93151-6
42. Heine L, Tillmann B, Hauet M, et al. Effects of preference and sensory modality on behavioural reaction in patients with disorders of consciousness. *Brain Inj*. 2017;31(10):1307–1311. doi:10.1080/02699052.2017.1306108
43. Cheng L, Cortese D, Monti MM, et al. Do Sensory Stimulation Programs Have an Impact on Consciousness Recovery? *Front Neurol*. 2018;9:826. doi:10.3389/fneur.2018.00826
44. Magee WL. Music in the diagnosis, treatment and prognosis of people with prolonged disorders of consciousness. *Neuropsychol Rehabil*. 2018;28 (8):1331–1339. doi:10.1080/09602011.2018.1494003
45. Carrière M, Larroque SK, Martial C, et al. An Echo of Consciousness: brain Function During Preferred Music. *Brain Connect*. 2020;10 (7):385–395. doi:10.1089/brain.2020.0744
46. Boly M, Faymonville ME, Peigneux P, et al. Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. *Arch Neurol*. 2004;61(2):233–238. doi:10.1001/archneur.61.2.233
47. Boly M. Measuring the fading consciousness in the human brain. *Curr Opin Neurol*. 2011;24(4):394–400. doi:10.1097/WCO.0b013e328347da94
48. Heine L, Castro M, Martial C, Tillmann B, Laureys S, Perrin F. Exploration of Functional Connectivity During Preferred Music Stimulation in Patients with Disorders of Consciousness. *Front Psychol*. 2015;6:1704. doi:10.3389/fpsyg.2015.01704
49. Lundström S, Twycross R, Mihalyo M, Wilcock A. Propofol. *J Pain Symptom Manage*. 2010;40(3):466–470. doi:10.1016/j.jpainsymman.2010.07.001
50. Shine JM, Lewis LD, Garrett DD, Hwang K. The impact of the human thalamus on brain-wide information processing. *Nat Rev Neurosci*. 2023;24 (7):416–430. doi:10.1038/s41583-023-00701-0
51. Van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. *Brain Res Brain Res Rev*. 2002;39(2–3):107–140. doi:10.1016/s0165-0173(02)00181-9
52. Zhang J, Zhang H, Yan F, et al. Investigating the mechanism and prognosis of patients with disorders of consciousness on the basis of brain networks between the thalamus and whole-brain. *Front Neurol*. 2022;13:990686. doi:10.3389/fneur.2022.990686
53. Edelman GM. Naturalizing consciousness: a theoretical framework. *Proc Natl Acad Sci U S A*. 2003;100(9):5520–5524. doi:10.1073/pnas.0931349100