

Original Article

Bispectral index-guided dexmedetomidine sedation during subthalamic nucleus deep brain stimulation surgery

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Abstract: Dexmedetomidine sedation is generally considered a safe and effective anesthesia method. However, successfully controlling a patient's anxiety, tension, and discomfort is still a challenge when using dexmedetomidine sedation during deep brain stimulation surgery. 31 patients with Parkinson's disease who were undergoing subthalamic nucleus deep brain stimulation treatment were enrolled in this study. Randomized case-control analysis was conducted with a local anesthesia (LA) group (n = 16) and a dexmedetomidine sedation (DEX) group (n = 15). The sedation protocol used bispectral index (BIS) feedback to guide the low-dose dexmedetomidine administration process. The indicators used for comparison between the 2 groups of patients undergoing deep brain stimulation surgery included: discomfort degree, blood pressure control, amplitude of neuronal firing suppressed during microelectrode recording, as well as complications of intracranial hemorrhage, confusion, and seizure. The mean visual analog scale (VAS) score of discomfort degree in the DEX group was 2.33 ± 0.816 , which was lower than that of the LA group (4.06 ± 0.68) ($P = 0.000$). The mean arterial pressure in the 2 groups was below 95 mmHg and decreased during the deep brain electrode implantation compared with the baseline value. One elderly patient with an inhibited microelectrode recording was identified in the DEX group, and one case of intracranial hemorrhage was identified in the LA group, with no other complications. BIS-guided dexmedetomidine sedation can significantly improve patients' comfort and meet blood pressure requirements during deep brain stimulation surgery, compared with local anesthesia. Elderly patients with Parkinson's disease require a reduced dose of dexmedetomidine.

Keywords: Dexmedetomidine, bispectral index, parkinson's disease, deep brain stimulation

Introduction

Subthalamic nucleus deep brain stimulation (STN DBS) has been widely accepted as an effective treatment for advanced Parkinson's disease. However, successfully controlling a patient's anxiety, tension, and discomfort during DBS surgery still remains a challenge for the anesthesiologist. Furthermore, electrode insertion into the deep brain nucleus requires blood pressure control in order to reduce the risk of intracranial hemorrhage during microelectrode targeting. Dexmedetomidine sedation is generally considered a safe and effective anesthesia method. However, the administration of dexmedetomidine varied significantly in previous studies [1-7], with loading doses ranging from 0.5 to 1.0 $\mu\text{g}/\text{kg}$ and maintenance doses ranging

from 0.1 to 1.0 $\mu\text{g}/\text{kg}/\text{min}$. During dexmedetomidine sedation, deep sedation affects the neuronal discharge of the subthalamic nucleus and interferes with electrode positioning [7]. The bispectral index (BIS) and Ramsay Sedation Scale (RSS) are commonly used to evaluate sedation depth. Research [2] has shown that when the BIS was less than 80, the microelectrode recording of the subthalamic nucleus may be inhibited. In order to meet the sedation demands of the surgery, we designed a BIS-guided low-dose dexmedetomidine administration process, and used a randomized case-control study to observe patients' comfort, microelectrode recording inhibition, and blood pressure control during electrode implantation in deep brain stimulation surgery.

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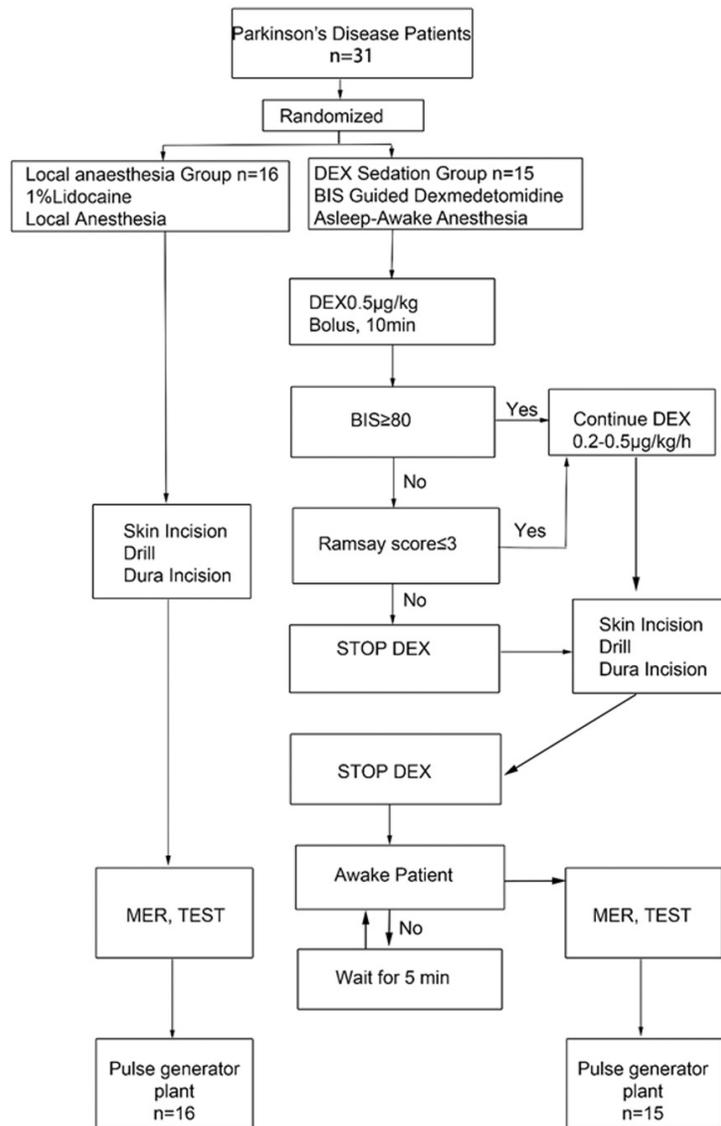


Figure 1. Protocol for intraoperative management. DEX: dexmedetomidine; BIS: bispectral index; MER: microelectrode recording; TEST: Clinical testing.

Materials and methods

Parkinson's disease patients undergoing deep-brain electrical stimulation surgery with a subthalamic nucleus target were included in the study. Patients excluded were those with BMI ≤ 18.5 kg/m², BMI ≥ 30 kg/m², chronic obstructive pulmonary disease, coronary heart disease, diabetes mellitus, grade II or III atrioventricular block, liver or kidney dysfunction, or use of antidepressants, and those older than 80 years of age, as well as those who refused to participate. All patients admitted to the study

signed informed consent forms. The study was approved by the Capital Medical University Xuanwu Hospital Ethics Committee and was conducted in May 2016. The clinical trial registration number was ChiCTR-IOR-16008464.

Surgical methods

All patients underwent nuclear magnetic resonance examination 1 day prior to surgery to determine the target location. On the morning of surgery, under local anesthesia with 1% lidocaine, the patient's head was fixed in a Cosman-Robert-Wells head frame, a computed tomography (CT) examination was performed, and the subthalamic nucleus target was calculated through the reconstruction of nuclear magnetic images. After the patient entered the operating room, his or her head was fixed to the surgical bed with the head frame. The neurosurgeon located the surgical incision site, cut the scalp at the site, drilled the skull, and cut open the dura mater (dura incision). A neurophysiology physician used a 200-600 k Ω platinum/iridium electrode (Bowdoinham, ME, USA) for microelectrode recording (MER) to determine whether the target position had reached the subthalamic nucleus.

After the microelectrode recording had determined the targeted motor region, the neurosurgeon implanted a stimulation electrode for clinical testing. The stimulation device was a 4-point electrode (Medtronic 3389, USA). The stimulation frequency was 130-180 Hz, the wave width was 60 μ s, and the stimulation voltage was 1-5 V. When the appropriate current intensity was administered, the patient's tremor or stiffness symptoms improved, indicating that the therapeutic target was accurate. Meanwhile, the neurophysiology physician determined whether the microelectrode recording

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Table 1. Demographic data, basal MAP, and the amount of preoperative Levodopa used in the 2 study groups

	DEX Group	LA Group	P-value
Age (y)	60.20 ± 8.40	58.38 ± 7.23	0.521
Weight (kg)	68.00 ± 9.44	62.84 ± 10.78	0.168
Sex (M/F)	10/5	12/4	0.556
MAP (mmHg)	90.24 ± 8.38	89.33 ± 9.10	0.478
Levodopa (mg)	516.67 ± 194.03	566.47 ± 191.58	0.774
Operation time (min)	82.53 ± 21.76	83.06 ± 32.32	0.958

DEX: dexmedetomidine, MAP: baseline mean blood pressure, Levodopa: preoperative levodopa dosage, Operation time: time from surgical incision to stimulation test completion.

was affected by the depth of sedation and whether the stimulation test was satisfactory.

Anesthesia methods

All patients fitted with head frames were brought into the operating room. An 18 G catheter was placed in the upper-limb peripheral vein, and ECG, non-invasive cuff blood pressure, and pulse oxygen saturation monitoring were established.

The patients were randomly divided into a dexmedetomidine sedation (DEX) group and a local anesthesia (LA) group using Excel software-generated random numbers. The bispectral index (Aspect, Vista Application Revision: 3.20, USA) was used to monitor the patient's sedation level in the DEX sedation group, and electrode pads were affixed to the forehead. After the patient's extracranial frame was fixed to the operating bed, the dexmedetomidine bolus was started immediately. The loading dose was 0.5 µg/kg, and an intravenous pump bolus was administered for 10 min. After the pump bolus was finished, the continuous infusion dose was adjusted to 0.2-0.5 µg/kg/min, according to the procedure (**Figure 1**). After shallow sedation was achieved, the skin incision was made. The dexmedetomidine bolus was stopped after the drilling had been completed. The patient was awakened during microelectrode recording and stimulation testing. If the patient could not be awakened during the test, we waited until the patient had awakened. The LA group received scalp 1% lidocaine local infiltration, but no sedative drugs.

The BIS was used to continuously monitor dexmedetomidine sedation. This information was recorded and evaluated using the RSS after the

completion of the dexmedetomidine bolus. Oxygen masks with a flow of 3 L/min were used during deep-brain electrode implantation. During microelectrode implantation, antihypertensive therapy consisted of 0.5 mg/kg esmolol (when the heart rate was greater than 60 beats/min) and 5 mg urapidil (when the heart rate was less than 60 beats/min), maintaining an average arterial pressure targeted below 95 mmHg. If hypotension occurred, with systolic blood pressure less than

90 mmHg or mean arterial pressure less than 60 mmHg, 50 µg phenylephrine was administered during each episode. If bradycardia occurred, 0.5 mg atropine was administered. The degree of discomfort during the deep-brain electrical stimulation procedure was assessed using the 10-degree visual analog scale (VAS: 0, no discomfort; 10, absolute discomfort) [5] prior to pulse generator implantation.

Data collection

Data collected included the patient's age, gender, height, weight, approximate disease onset date, Levodopa dosage, and other general information. Main end events included the VAS score of discomfort in patients undergoing deep brain stimulation and the number of patients with microelectrode recording inhibition. Secondary clinical indicators included the recorded RSS of baseline (T1), drilling (T2), left-side electrode placement (T3), and right-side electrode placement (T4), as well as the mean arterial pressure (MAP), heart rate (HR), and pulse oxygen saturation (S_pO_2). Additionally, we recorded perioperative surgery-related complications such as intracranial hemorrhage, confusion, and seizure. BIS values were continuously collected for all patients using the BIS monitor. Electroencephalograms (EEGs) were acquired from the BIS monitor.

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences, Windows version 16.0 (SPSS, Chicago, IL, USA). A *p*-value less than 0.05 was considered significant. Normality of the data distribution was assessed using the Kolmogorov-Smirnov test. MAP, HR, BIS, S_pO_2 , and VAS data with normal

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Table 2. Intraoperative MAP, HR, BIS, and S_pO₂ between the DEX and LA groups

Data	Time	DEX Group		p-value	DEX Group		LA Group	
		Mean, SD	Mean, SD		Min	Max	Min	Max
MAP	T1	98.07 ± 11.62	101.19 ± 8.79	0.404	76.00	117.00	85.00	120.00
	T2	91.40 ± 14.06	96.19 ± 10.55	0.290	71.00	126.00	80.00	118.00
	T3	86.13 ± 8.74 [§]	89.85 ± 6.87 [§]	0.228	63.00	95.00	77.00	99.00
	T4	84.73 ± 7.91 [§]	88.31 ± 8.57 [§]	0.276	72.00	100.00	69.00	106.00
HR	T1	79.27 ± 11.14	81.56 ± 13.29	0.607	58.00	97.00	62.00	108.00
	T2	72.13 ± 10.16	84.44 ± 12.48	0.006	44.00	83.00	63.00	104.00
	T3	72.83 ± 8.74	84.77 ± 12.42	0.011	52.00	82.00	64.00	112.00
	T4	74.80 ± 10.73	82.50 ± 14.43	0.104	50.00	99.00	56.00	116.00
BIS	T1	94.08 ± 4.09	93.46 ± 3.36	0.679	83.00	98.00	85.00	98.00
	T2	79.62 ± 10.10 [§]	91.46 ± 3.82	0.001	53.00	90.00	86.00	98.00
	T3	87.30 ± 6.96*	90.73 ± 4.29	0.186	74.00	96.00	83.00	98.00
	T4	84.38 ± 8.09 [§]	91.46 ± 4.65	0.012	68.00	97.00	85.00	98.00
S _p O ₂	T1	97.40 ± 1.40	98.25 ± 1.44	0.107	95.00	100.00	95.00	100.00
	T2	96.80 ± 2.31	97.50 ± 1.83	0.406	92.00	100.00	96.00	100.00
	T3	96.67 ± 2.06	97.15 ± 1.72	0.527	94.00	100.00	95.00	100.00
	T4	97.00 ± 1.96	97.43 ± 1.71	0.513	94.00	100.00	95.00	100.00

*P < 0.05 compared with the baseline (T1), [§]P < 0.01 compared with the baseline (T1). MAP: mean arterial pressure, HR: heart rate, BIS: bispectral index, S_pO₂: pulse oxygen saturation. Data were expressed as mean ± SD, minimum, maximum. T1: baseline; T2: drilling; T3: left side electrode placement; T4: right side electrode placement.

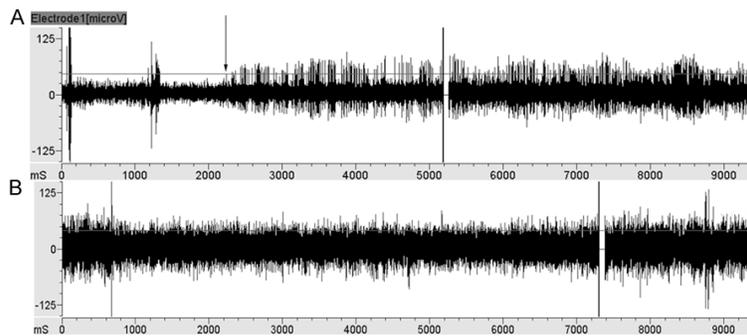


Figure 2. A case of microelectrode recording under dexmedetomidine sedation. During the recording period, the patient had a BIS of 65 and an RSS of 5 (A). The arrow indicates the potential change recorded by the microelectrode after entering the subthalamic nucleus. The firing rate increased sharply after the patient awoke (B). (A) Sedated state, (B) Waking state.

distributions were expressed as mean ± standard deviation. Maximum and minimum values of MAP, HR, BIS, and oxygen saturation were also recorded for the 2 groups. These data were compared using the Independent Samples t-test. Repeated measurement data within groups were analyzed by the one-way analysis of variance (ANOVA) followed by the least significant differences (LSD) method. Fisher's exact test was used to compare DBS surgery complications. Pearson correlation analysis was conducted for the BIS and RSS.

Results

Demographics and baseline characteristics

A total of 31 patients with Parkinson's disease were included in this study, including 6 cases of unilateral deep-brain electrical stimulation and 25 cases of bilateral deep-brain stimulation. No cases were excluded. After random grouping, there were 15 patients in the dexmedetomidine (DEX) sedation group and 16 cases in the local anesthesia (LA) group. There was no significant

difference in general information between the 2 groups, and there was no difference in basal blood pressure, approximate date of disease onset, or amount of preoperative Levodopa used (Table 1).

Deep brain stimulation surgical results

There were 3 cases of unilateral electrode implantation and 12 cases of bilateral electrode implantation in the DEX group, and 3 cases of unilateral electrode implantation and 13 cases

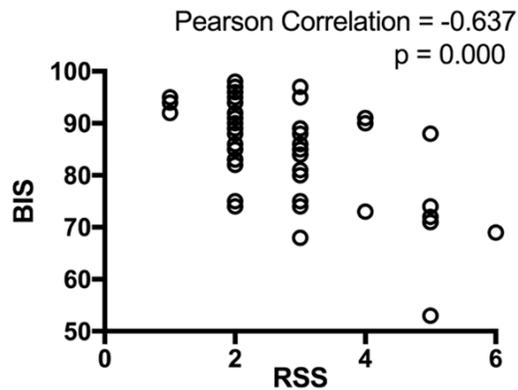


Figure 3. Correlation between the BIS and RSS in the DEX group. Pearson $r = -0.637$, $P = 0.000$. BIS: bispectral index, RSS: Ramsay Sedation Scale.

of bilateral electrode implantation in the LA group. During the stage of deep brain stimulation, the operation time from surgical incision to stimulation test completion was 82.53 ± 21.76 min in the DEX group, which did not differ significantly from that of the LA group (83.06 ± 32.32 min, $P > 0.05$; **Table 1**). Microelectrode recording and positioning was performed on each side of the subthalamic nucleus in all patients. There were 2 cases of microelectrode adjustment in the LA group; the microelectrode positions of the remaining cases were satisfactory.

There was 1 case of intracranial hemorrhage, confirmed by postoperative CT, in a 52-year-old male patient in the LA group (1/16), which had improved at discharge after conservative treatment. This patient's preoperative mean arterial pressure in the ward was 97 mmHg, and up to 114 mmHg during the drilling. After being administered 320 mg esmolol and 40 mg urapidil, the mean arterial pressure on both sides during the drilling was 87-89 mmHg. There were no cases of intracranial hemorrhage in the DEX group (0/15, $P > 0.05$ compared with LA group). No other patients in the 2 groups experienced complications.

Anesthesia management results

15 patients were managed using BIS and RSS evaluations. 5 cases required the infusion of only a single loading dose and 10 cases needed a loading dose plus continuous infusion. The continuous infusion time was 30.40 ± 7.01 min after administration of the loading dose.

During deep brain stimulation, the VAS score of the DEX group had a mean value of 2.33 ± 0.82 . This was lower than the 4.06 ± 0.68 value of the LA group ($P = 0.000$). The mean arterial pressure in the 2 groups was less than 95 mmHg and decreased during deep-brain electrode implantation compared with the baseline value ($P < 0.01$). There was no significant difference in mean arterial pressure between the 2 groups during deep-brain electrode implantation (**Table 2**). A 77-year-old in the DEX group experienced a subthalamic nucleus microelectrode recording inhibition; the BIS showed a burst suppression. The amplitude of subthalamic nucleus firing increased after the patient was awakened. This event did not affect the determination of the targeted subthalamic nucleus (**Figure 2**).

As expected, the BIS was significantly lower in the DEX group than in the LA group at the time of drilling. This study found that dexmedetomidine loading dose administration reduced the BIS from 94 to a minimum of 53 over 10 min. An unexpected result was that the BIS remained lower in the DEX group after the right electrode was implanted. The mean heart rate was lower in the DEX group than in the LA group at the time of skull drilling and left electrode implantation. There was no significant difference between the 2 groups in oxygen saturation during drilling and electrode implantation (**Table 2**). There was also no significant difference in administration of the antihypertensive drugs urapidil (DEX 46.7% vs. LA 75.0%, $P = 0.149$) or esmolol (DEX 40.0% vs. LA 56.2%, $P = 0.479$).

We collected 57 pairs of BIS and RSS data and found that the 2 variables were negatively correlated, $R = -0.637$ (**Figure 3**). The mean RSS of the DEX group was 3.17 ± 1.03 at the time of left electrode insertion and 3.08 ± 1.31 at the time of right electrode insertion.

One patient receiving a $0.5 \mu\text{g}/\text{kg}$ dose of dexmedetomidine was observed to have an inhibition of subthalamic nucleus discharge. We observed burst suppression after administration of the dexmedetomidine bolus (**Figure 4**) in this patient. From the trend graph, it can be seen that when the BIS was below 70, the EMG also decreased significantly, which may have led to the lessening of the patient's tremor symp-

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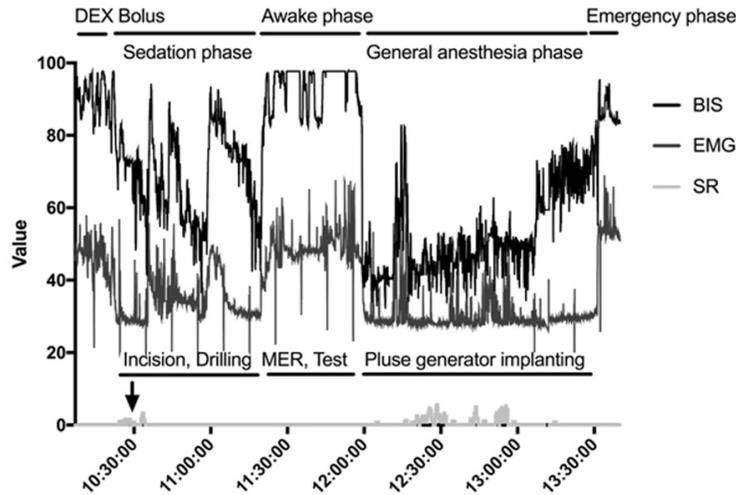


Figure 4. A typical case of continuous monitoring of BIS, EMG, and SR trends during deep brain stimulation surgery. 24 min after dexmedetomidine (0.5 $\mu\text{g}/\text{kg}$) administration, the patient fell asleep; at this time, BIS = 50 and RSS = 4. During drilling, the BIS value increased after the patient was awakened. Before MER, the patient was awakened, the BIS value rapidly increased, and MER and TEST were successfully completed. This shows that the EMG decreases during dexmedetomidine sedation, suggesting that dexmedetomidine may reduce EMG activity via deep sedation. Burst suppression (\downarrow) was observed simultaneously with dexmedetomidine deep sedation.

toms. Therefore, the stimulation test was delayed, but the MER and stimulation test results of the patient were not affected. Additionally, we also found that in 5/15 cases of the DEX group, when the patients opened their eyes by themselves the BIS EEG exhibited an “eye blink wave”, which was consistent with blinking. When the patients entered a shallow sedation state, their eyes closed and the “blink wave” disappeared (Figure 5), accompanied by a decrease in the BIS value.

Discussion

Dexmedetomidine is an α_2 -adrenergic receptor agonist, which mainly acts on the central locus coeruleus and spinal cord α_2 receptor, resulting in a sedative and analgesic effect. It is widely used in deep-brain electrical stimulation, and its safety and effectiveness have been fully confirmed [1, 2, 5, 7-15]. In particular, its respiratory safety is superior to that of propofol. According to the results of a literature review [16], the dexmedetomidine ED_{95} is 0.38 $\mu\text{g}/\text{kg}$ for those older than 65 years and 0.57 $\mu\text{g}/\text{kg}$ for those aged 45 to 64 years. Since the average ages of the patients included in this study

were 60.20 years (DEX group) and 58.38 years (LA group), we used 0.5 $\mu\text{g}/\text{kg}$ as the initial loading dose. A previous study had suggested that a BIS lower than 80 can inhibit microelectrode recording [2]. Deep sedation with dexmedetomidine can reduce the firing rate of target nuclei [11], but one study found that dexmedetomidine increased the subthalamic nucleus discharge frequency [7]. In addition, either the RSS [5, 13] or the Observer's Assessment of Alertness/Sedation (OAA/S) [1, 11] is commonly used to monitor sedation during deep-brain electrical stimulation, controlling for an RSS ≤ 3 or an OAA/S ≥ 3 . Since the RSS is based on the patient's response to the environment and the BIS is based on EEG analysis, the combination of the 2 methods can improve the monitoring accuracy

of dexmedetomidine sedation. By monitoring the BIS and RSS in ICU patients, one study [17] discovered that when the RSS = 3, the BIS was 81.42 ± 14.85 . Therefore, for sedation management designed to control a patient in a shallow sedation state, the initial threshold of the BIS was set to 80 and the RSS was set to 3.

The overall VAS discomfort score of the DEX group during drilling and electrode implantation was lower than that of the LA group, demonstrating the effectiveness of dexmedetomidine sedation. After dexmedetomidine sedation, there was no significant difference in blood pressure during drilling and electrode implantation compared to the LA group. There was also no significant difference in the administration of antihypertensive drugs. The mean arterial pressure during electrode implantation was less than 95 mmHg. This finding indicates that dexmedetomidine does not reduce the need for antihypertensive drugs, though this may be due to the low dose of dexmedetomidine that was used. This is consistent with the results of previous research [6]. Dexmedetomidine sedation also had a significant effect on heart rate. Dur-

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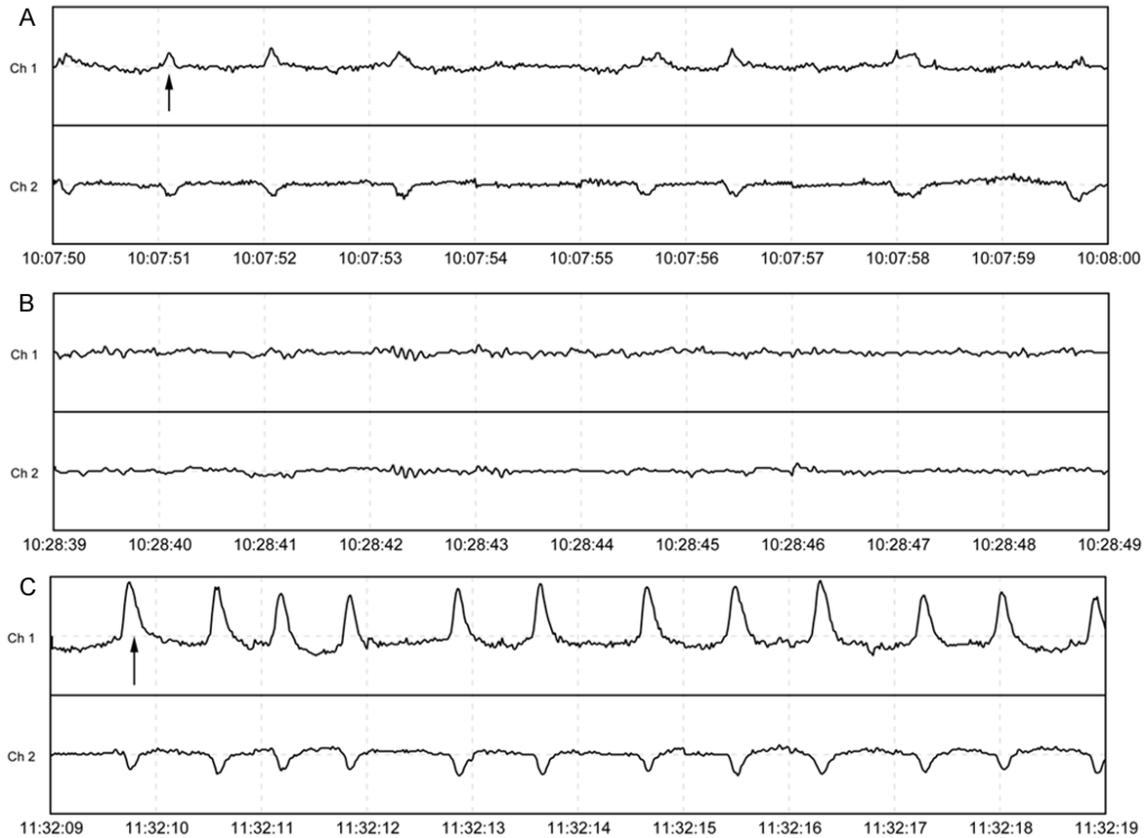


Figure 5. Eye blink wave in electroencephalogram, 50 µv/division. A. Before the sedation, patient awake; BIS = 97 and RSS = 2. EEG showed an eye blink wave (↑) and blink synchronization. B. After 13 min of 0.5 µg/kg DEX infusion, BIS = 73, RSS = 4, the “blink wave” disappeared. C. After awakening, the “blink wave” was recovered (↑); BIS = 97.7, RSS = 2. BIS: bispectral index, RSS: Ramsay Sedation Score.

ing drilling, the heart rate in the sedation group was lower than that in the LA group, with a minimum value of 44 beats per minute. Past research [18] has shown that the heart rate was less than 50 beats per minute during dexmedetomidine infusion. Therefore, attention should be paid to hemodynamic changes during dexmedetomidine sedation in Parkinson's disease patients.

In this study, the discharge of the subthalamic nucleus could be inhibited when deep sedation occurred in a Parkinson's patient (Figure 2). However, the inhibition due to dexmedetomidine was reversible. The sedation effect of dexmedetomidine is dose-dependent and characterized by natural non-rapid eye movement sleep [19], as well as the existence of a wake-up system function. We therefore speculate that dexmedetomidine has an indirect inhibitory effect on the electrical activity of subthalamic nucleus neurons, which can be reversed after awakening.

The dexmedetomidine loading dose helps to relieve the discomfort caused by surgical procedures such as skin incision, drilling, and dura incision. Thus, we recommend the infusion of a dexmedetomidine loading dose 10 min before skin incision. A previous study [16] found that a single dose of less than 0.5 µg/kg could ensure a sedation time of 30 min, and some patients with only unilateral deep-brain electrical stimulation were given only a loading dose to meet the sedation requirement. In this study, we found that dexmedetomidine still had a sedation effect during the MER and stimulation test stages, with minimum BIS values of 74 and 68, respectively (Table 2). Therefore, dexmedetomidine administration should be stopped after drilling. Another study [8] recommends stopping drug infusion at least 15 minutes before MER. In addition, we observed that the microelectrode recording of an elderly patient was inhibited after the application of dexmedetomidine (Figure 2). A previous investigation had

shown that up to 46% of elderly patients have RSS values of 5-6 from a 0.5 µg/kg bolus [14]. Also, an age greater than or equal to 64 years is an independent risk factor for postoperative complications in patients with Parkinson's disease [6, 10]. Therefore, the single loading dose of dexmedetomidine should be reduced in elderly patients. Moreover, since research [20] has also indicated that dexmedetomidine administered at a rate of 0.2 µg/kg/min for 30 min can reduce cerebral blood flow, it is important to avoid hypotension during deep brain stimulation in elderly patients with Parkinson's disease. In addition, since hypertension can cause intracranial hemorrhage, reducing blood pressure fluctuations by effectively controlling pain and tension during deep brain stimulation is of particular importance.

In this study, the BIS and RSS were significantly negatively correlated. The monitoring reliability of dexmedetomidine sedation depth has been reported using the bispectral index [18, 21, 22]. In this study, we found that BIS monitoring could assess patients' anxiety states, and BIS-acquired forehead EEGs showed potential changes synchronized with eye blink waves, which disappeared after the patient fell asleep, suggesting that BIS EEG changes are an effective method of judging the sedation effect. Therefore, anesthesiologists need to pay attention not only to changes in BIS values, but also to changes in EEGs, to ensure an accurate analysis of the patient's sedation depth. Compared to the traditional sedation standard of an RSS = 3, administering sedative treatment under the guidance of BIS monitoring was more secure and effective. Previous research [17] has found that an RSS of 3 corresponds to a BIS value of 81.4 ± 14.9 . It is apparent that the BIS has a broader range of values than the RSS and can better quantify the level of sedation, while the RSS scoring system can reduce the error of BIS variations in sedation level monitoring. Therefore, the combined application of the RSS and BIS is an effective method for monitoring sedation.

This study has a few limitations: (1) It was conducted in a single center, with relatively few cases; (2) No blind method was used in the safety assessment of dexmedetomidine; (3) The firing frequency of subthalamic neurons was not quantified. Our study did not track the

changes in BIS, MAP, HR, or S_pO_2 parameters over time, instead using surgical procedures as observational time points, since all patients' operations were relatively consistent. The main goal of our study was to observe changes in the parameters at various surgical time points, since it was easy to grasp the patient's sedation and physiological states during surgery after the administration of dexmedetomidine, thus helping us to better evaluate the effect of dexmedetomidine sedation.

In conclusion, our study results suggest that the use of BIS-guided dexmedetomidine sedation can improve patient comfort and meet blood pressure requirements during microelectrode recording, compared to local anesthesia. In addition, elderly patients with Parkinson's disease require a reduced dose of dexmedetomidine.

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Disclosure of conflict of interest

None.

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