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RESEARCH

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Effects of mild cognitive impairment and sleep disorders on the minimum alveolar concentration value of sevoflurane

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Abstract

Objectives To explore the effect of mild cognitive impairment (MCI) and MCI with sleep disorders on the potency of sevoflurane anesthesia in the elderly.

Design Prospective study methods. Dixon up-and-down methods.

Setting Comprehensive public tertiary hospital, Cangzhou City, Hebei Province, China.

Participants 70 elderly patients scheduled for elective unilateral breast cancer surgery and finally analyzed 58 patients, including 30 patients with MCI (group M) and 28 patients with MCI with sleep disorders (group MS).

Outcome measures The required minimum alveolar concentration (MAC) value of sevoflurane in the two groups was determined using the Dixon up-and-down method. The MAC value of sevoflurane and its 95% confidence interval (CI) were calculated using the logistic regression method. Serum melanin-concentrating hormone concentrations were determined by Elisa kits.

Results The MAC value of sevoflurane in group M was 1.43 (95% CI 1.05–1.61%), and the MAC value of sevoflurane in group MS was 1.93 (95% CI 1.78–2.08%), There were notable differences between the two groups ($P < 0.0001$). The level of melanin-concentrating hormone (MCH) in the MS group was significantly lower than that in the M group (21.52 ± 3.82 vs. 37.17 ± 3.66 pg/ml, $P < 0.0001$). There was a significant negative correlation between MCH levels and the probability of body movement during skin incision (OR = 0.844, 95% CI: 0.715–0.996, $P = 0.045$).

Conclusions Patients with MCI with sleep disorders required higher doses of sevoflurane than those with MCI alone. Changes in anesthetic requirements may be related to changes in MCH levels.

Keywords Sevoflurane, Minimum Alveolar Concentration, Mild Cognitive Impairment, Sleep Disorder, Melanin-concentrating Hormone, Dixon Up-and-down

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Introduction

Mild cognitive impairment (MCI) is characterized by impairment in one or more cognitive domains, which may lead to difficulties in daily functioning while still maintaining independence and autonomy [1]. MCI occurs mostly in elderly patients, and the overall prevalence of MCI in China is about 15.5%. With the progression of symptoms, MCI gradually transitions into Alzheimer's disease (AD), amplifying the mental distress and financial burden on patients and their families [2, 3]. There is an urgent need to delay the progression of MCI.

In clinical observation, it has been found that sleep disorders are common in the elderly, such as insomnia, sleep fragmentation, and sleep structure disorders [4, 5]. Preoperative sleep disorders typically have an impact during the perioperative period [6], which may greatly change the dose of intraoperative anesthetics. Studies have shown that patients with preoperative sleep disorders have an increased demand for propofol during a painless gastroscopy, leading to higher plasma concentrations and infusion rates per unit of body surface area [7]. But, there is still little evidence on the dosage of general anesthetics for longer surgeries.

Melanin-concentrating hormone (MCH) is an important neuroregulatory hormone involved in controlling the wake-sleep cycle [8, 9]. Animal experiments have shown that impaired function of the MCH system in mice leads to abnormal excitatory drive and sleep defects [10]. However, the relationship between MCH and human sleep remains unclear.

Based on the above considerations, we hypothesized that the MAC values of sevoflurane differ between patients with MCI and those with MCI with sleep disorders, and that these values correlate with serum MCH levels. Therefore, we investigated the optimal intraoperative concentration of sevoflurane in patients with MCI and MCI with sleep disorders. We also analyzed the relationship between MCH and body movement response to sevoflurane anesthesia using logistic regression.

Methods

Participating patients

This clinical study was reviewed and approved by the Ethics Committee of Cangzhou Central Hospital (2021-206-02 (z)). Before conducting the study, the patients and their families were fully informed and signed an informed consent form. Patients aged 60–75 years with a body mass index (BMI) of 18.5–23.9 kg/m^2 were selected for unilateral radical mastectomy between January 2023 and December 2023. ASA I or II, with no visual or hearing impairments.

Patients were excluded if they met any of the following criteria: refusal to sign informed consent, long-term use of analgesics, recent use of anesthetics and psychiatric drugs, history of alcohol and drug abuse, liver and kidney dysfunction, electrolyte disturbance, concomitant diseases of other important organs, contraindication to inhaled anesthetics, and family history of malignant high fever.

Inclusion criteria for patients with mild cognitive impairment: (1) Minimum Mental State Examination (MMSE) < 27; (2) Montreal Cognitive Assessment (MoCA) < 26 [11].

Inclusion criteria for patients with sleep disorders: (1) Pittsburgh Sleep Quality Index [12] (PSQI) ≥ 7; (2) Epworth Sleepiness Scale [13] (ESS) ≥ 10.

Methods of anesthesia

All patients were strictly fasted before surgery. Upon entering the room, the individual inhaled oxygen through the mask, established peripheral venous access, and infused lactated Ringer's solution at a rate of 10 ml/kg. Non-invasive blood pressure (NIBP), electrocardiogram (ECG), pulse oxygen saturation (SPO2), end-tidal carbon dioxide concentration (ETCO2), and nasopharyngeal temperature were monitored. Sevoflurane was used for anesthesia induction. The sevoflurane volatile tank scale was adjusted to 8%, the oxygen flow rate was set to 6 L/min, and the anesthesia circuit was pre-filled. At the beginning of the induction, the mask was tightly fastened to the patient's face, and the patient was instructed to take deep breaths. After the patient lost consciousness, their jaw relaxed, and a laryngeal mask was inserted for mechanical ventilation. Tidal volume was 6–8 ml/kg, respiratory rate 10–12 breaths/min, inspiratory/expiratory ratio 1:2, oxygen flow 2 L/min, and ETCO2 was maintained at 30–40 mmHg. Bispectral index (BIS) was used in all patients to maintain BIS values between 40 and 60.

In this study, the Dixon up-and-down method was used to set the end-tidal sevoflurane concentration of the first patient in each group to 2.2%. When the concentration reached the set value and remained stable for at least 15 min, the skin incision was initiated. Conversely, if a body movement response was recorded as positive, the end-tidal sevoflurane concentration was increased by 0.2% in the next patient. The midpoint between a negative reaction and the first subsequent positive reaction was recorded as the equilibrium point. According to the Dixon up-and-down method guidelines [14], we randomly assigned patients to groups for experiments. The experiment concluded when there were 7 equilibrium points, ensuring that the number of patients in each group exceeded twenty.

Measurement of melanin-concentrating hormone

Three milliliters of venous blood were collected from the patient before the surgery. The blood was then centrifuged at 3,000 rpm for 15 min, and the upper layer of serum was collected post-centrifugation. The serum was stored in a refrigerator at -80 °C. Serum melanin-concentrating hormone concentrations were determined by Elisa kits (Cusabio Biotechnology Co., China).

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. Measurement data following normal distribution were presented as mean ± standard deviation ($\bar{x} \pm s$), and a two-sample t-test was employed to compare between groups. Non-normally distributed measurement data were expressed as median (M) and interquartile range (IQR). The MAC value and the 95% confidence interval (CI) of sevoflurane were calculated by the probit analysis. Logistic regression was conducted to test the correlation of probability of MAC and melanin-concentrating hormone. $P < 0.05$ was considered statistically significant.

Results

A total of 58 people participated in the entire experiment (Fig. 1). Seventy patients were screened for mild cognitive impairment using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scales. Thirty patients with sleep disorders were screened using the Pittsburgh Sleep Quality Index (PSQI) and the Epworth Sleepiness Scale (ESS). Nine patients were excluded from the experiment: five refused

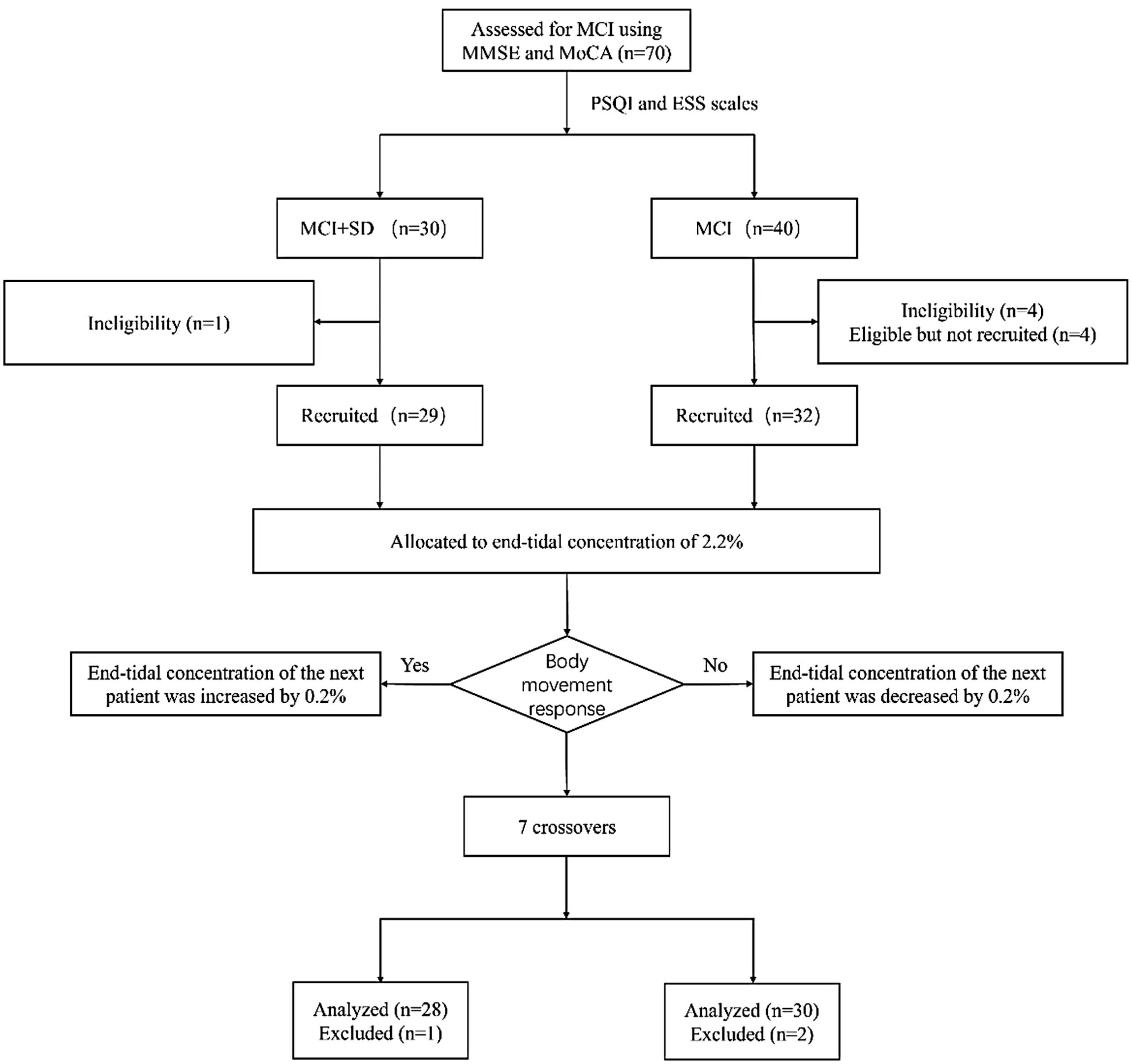

Fig. 1 Flow chart of the experiment

Table 1 Subject characteristics and concentration of MCH

Parameters	M group ($n=30$)	MS group ($n=28$)	P value
Age (years)	66.50 ± 2.93	65.07 ± 4.37	0.147
Height (cm)	159.40 ± 4.12	160.7 ± 4.51	0.264
Body weight (kg)	57.40 ± 5.37	59.61 ± 4.37	0.093
BMI (kg/m^2)	22.55 ± 1.39	23.06 ± 0.85	0.099
ASA	I~II	I~II	
Education years (years)	5.93 ± 1.36	6.04 ± 1.11	0.756
MCH (pg/ml)	37.17 ± 3.66	21.52 ± 3.82	< 0.0001

MCH: Melanin-concentrating hormone

to sign informed consent, two had a BMI < 18.5, one had a BMI > 23.9, and one had severe anemia. Additionally, three patients were excluded from data analysis: two had intraoperative use of vasoactive agents, and one had a laryngeal mask placement time exceeding 30 s. Patients were assigned to two groups: the MCI group (M, $n=30$) and the MCI + SD group (MS, $n=28$).

The age, height, body weight, BMI, ASA rating, and education years were compared between the two groups, and there was no significant difference. Serum MCH levels were lower in patients with sleep disorders associated with MCI (Table 1).

In this study, the Dixon up-and-down method was used to explore the MAC value of sevoflurane in patients with MCI and MCI patients with sleep disorders. The dose of sevoflurane for the next patient was adjusted based on their body movement response during the skin incision. As shown in Fig. 2, the MAC value of sevoflurane in group M was 1.43 (95% CI 1.05–1.61%), and the MAC value of sevoflurane in group MS was 1.93 (95% CI

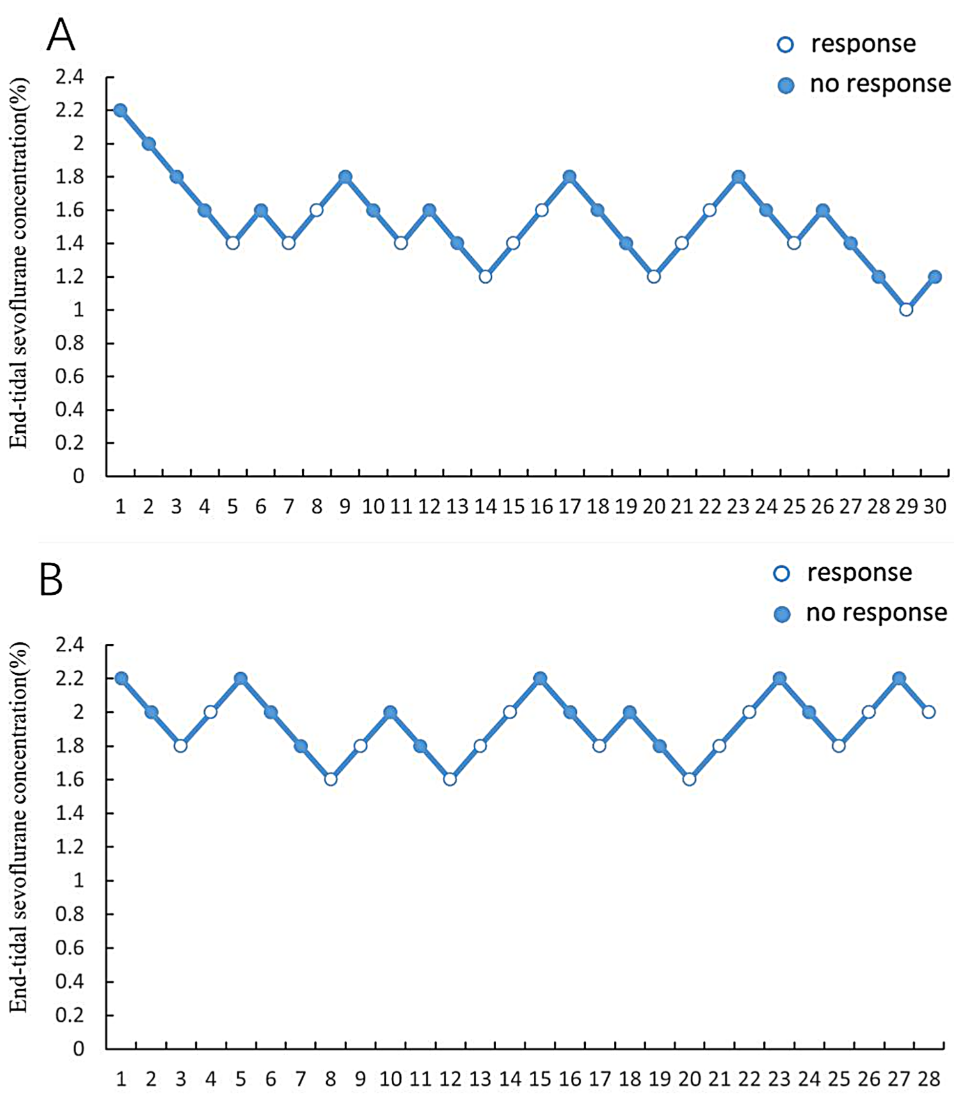

Fig. 2 Response of each subject to predetermined end-tidal sevoflurane concentrations. **A**: Sevoflurane MAC values in MCI patients; **B**: MAC value of sevoflurane in MCI patients with sleep disorders

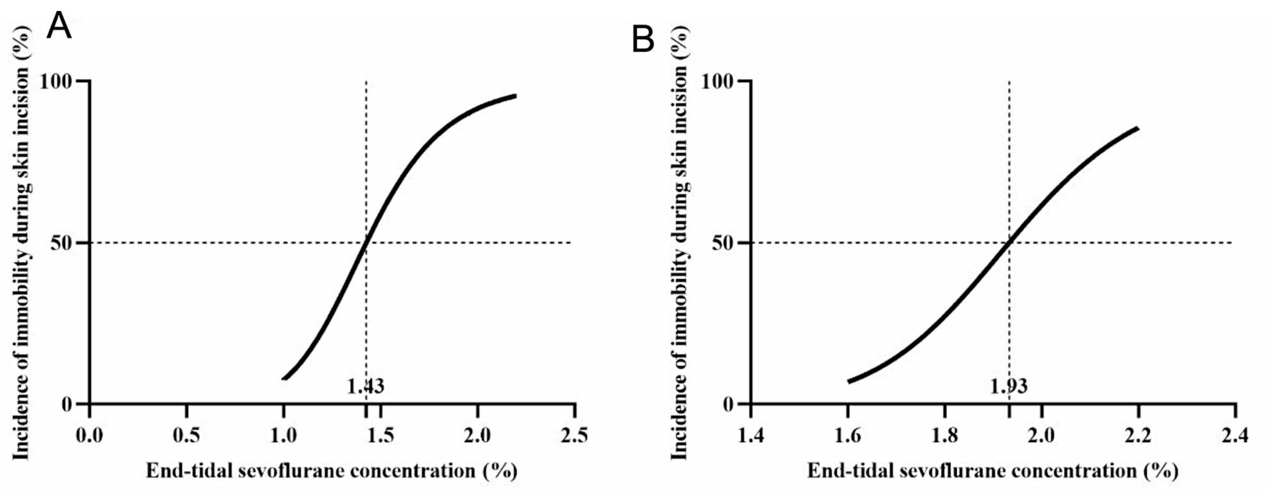

Fig. 3 Dose-response curves of end-tidal sevoflurane concentration versus body movement response to skin incision. **A**: Dose-response curves in group M; **B**: Dose-response curves in group MS

Table 2 Results of logistic regression analysis

Independent variable	Regression coefficient (β)	SE	OR	95% CI for OR	*P* value
MCH	-0.170	0.085	0.844	0.715–0.996	0.045
Constant	3.647	1.836	38.371		0.047

1.78–2.08%). Figure 3 illustrates the dose-response curve of body movement response to skin incision in relation to sevoflurane MAC value.

In this study, the logistic regression model indicated that MCH concentration was negatively correlated with the incidence of body movement response during skin incision. The logistic regression equation for predicting movement response was P(movement response) = 3.647–0.17MCH, with an odds ratio (OR) of 0.844 (95% CI 0.715–0.996, P = 0.045) (Table 2).

Discussion

Our study found that MCI patients with sleep disorders required higher sevoflurane MAC values and had lower serum MCH concentrations. Additionally, we confirmed the presence of a negative relationship between MCH and body movement responses.

MAC is a valid measure for evaluating the potency of volatile anesthetics [15]. Numerous studies have demonstrated that diseases can impact the MAC value of inhaled anesthetics, leading to variations from the typical MAC values in healthy individuals. Wu et al. [16] found that patients with end-stage renal disease had abnormal neurological function and a reduced requirement for sevoflurane compared to patients with normal renal function. Parkinson's disease (PD) is a neurodegenerative condition that is more common in elderly patients. Clinical evidence indicates that PD patients require lower concentrations of sevoflurane and propofol compared to non-PD patients [17, 18]. All the aforementioned studies have demonstrated that preoperative abnormalities or pathological conditions can impact the administration of intraoperative anesthetics. It is very important to determine the appropriate anesthetic dose for the patient to navigate the perioperative period smoothly [19]. MCI and sleep disorders frequently coexist in the elderly, and the impact of these two pathological conditions on the MAC value of sevoflurane remains uncertain. Therefore, we designed an experiment to explore the appropriate MAC value of sevoflurane in MCI patients and MCI patients with sleep disorders, and to compare them.

The sequential method was first used in anesthesia research. Since its development, it has become a classic method for exploring the median effective dose or MAC value of anesthetic drugs [14, 20]. In practice, the sequential method is mainly used for small sample designs. This study included a total of 58 patients, meeting the sample size requirements of the sequential method [14]. The sequential method required that the experiment should continue until at least six equilibrium points had occurred. We decided to end the experiment when seven equilibrium points had occurred, as stated in the published literature [21, 22]. In this study, the MAC value of sevoflurane was adjusted by observing the body movement response during skin incision. The results showed that the MAC value of sevoflurane in MCI patients was about 1.43, while in MCI patients with sleep disorders was about 1.93.

There is a strong association between MCH and sleep promotion [23]. Willie and his colleagues found that MCH knockout mice were awake and more active, exhibiting less non-REM sleep [24].Activation of mouse MCH neurons increased rapid eye movement (REM) sleep without altering other sleep states [25]. Neurons containing orexin or MCH intermingle with each other in the perifornix and lateral hypothalamus, and these neurons are independent of each other but project to similar target areas in the brain [26]. In orexin-deficient mice, the activation of MCH neurons also increased the abnormal intrusion of REM sleep, as evidenced by cataplexy and a short latency transition to REM sleep (SLREM) [25]. Previous studies have shown a positive association between plasma orexin-A and increased anesthetic requirements in young women with sleep disorders [27]. Therefore, we hypothesized that there was a correlation between MCH and sevoflurane MAC value, which was confirmed by experiments. Logistic regression analysis showed that serum MCH levels and the occurrence of body movement reactions during skin incision, which proved that MCH levels can impact the necessary sevoflurane MAC value for patients.

There are several other limitations of this study that need to be addressed. Firstly, the age inclusion criteria for this study were individuals aged 60–75 years. However, in clinical practice, there are still elderly patients over 75 years old, and the MAC will decrease significantly with every 10-year increase in age [28]. Therefore, to more accurately control the dosage of anesthetics in elderly patients, the MAC value can be adjusted based on age gradients. Secondly, sleep disorders are classified into many types. We only screened patients with sleep disorders using the scale and did not categorize them. Finally, we did not consider any hypnosedative medication taken by patients before surgery, the use of which may also have had an effect on sevoflurane MAC values.

In conclusion, our study showed that patients with MCI and sleep disorders required higher doses of sevoflurane than those with MCI alone. Furthermore, we found a correlation between serum MCH concentration and sevoflurane MAC value.

Abbreviations

MAC	Minimum alveolar concentration
CI	Confidence interval
MCH	Melanin-concentrating hormone
MCI	Mild cognitive impairment
AD	Alzheimer's disease
BMI	Body mass index
MMSE	Minimum Mental State Examination
MoCA	Montreal Cognitive Assessment
PSQI	Pittsburgh Sleep Quality Index
ESS	Epworth Sleepiness Scale
NIBP	Non-invasive blood pressure
ECG	Electrocardiogram
SPO_2	Pulse oxygen saturation
$ETCO_2$	End-tidal carbon dioxide concentration
BIS	Bispectral index
PD	Parkinson's disease

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Author contributions
W.L. : Conceptualization; Data Curation; Funding Acquisition; Formal Analysis; Methodology; Writing-Original Draft; Writing-Review&Editing Y.S. : Investigation; Validation; Writing-Original Draft; Writing-Review&Editing N.Z. : Investigation; Supervision; Writing-Original Draft; Writing-Review&Editing G.Y. : Formal Analysis; Visualization; Writing-Original Draft; Writing-Review&Editing.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate
This study involves human participants and the Institutional Review Board of Cangzhou Central Hospital (2021-206-02 (z)). This study was conducted in accordance with the principles set out in the Declaration of Helsinki for medical research involving human subjects. Informed consent was obtained from all participants and their legal guardians. The study adheres to CONSORT guidelines.

Consent for publication
Not Applicable.

Trial registration number
ChiCTR2400082114 (21/03/2024). The ethical approval of this study was approved by the Ethics Committee of Cangzhou Central Hospital on December 15, 2021.

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Competing interests
The authors declare no competing interests.

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