Clinical Interventions in Aging

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CLINICAL TRIAL REPORT

Effects of Remimazolam on Intraoperative Frontal Alpha Band Power Spectrum Density and Postoperative Cognitive Function in Older Adults Undergoing Lower Extremity Fractures Surgeries: A Randomized Controlled Trial

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Purpose: Low density of electroencephalogram alpha band power was reported to be associated with perioperative cognitive dysfunction. Few studies have conducted to explore the effects of remimazolam on intraoperative frontal alpha band power spectrum density in older adults. Here, we aimed to explore the impact of remimazolam on intraoperative frontal brain wave alpha band activity and postoperative cognitive function in older adults undergoing lower extremity fractures surgeries.

Methods: Patients undergoing elective general anesthesia for lower extremity fracture surgery were randomly allocated to remimazolam group (Group R) and midazolam group (Group M). Group R was induced with remimazolam bolus 0.1 mg/kg followed by a maintenance dose of 0.1 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for general anesthesia. Group M was induced with midazolam 0.05 mg/kg followed by normal saline maintenance of 0.1 $mL{\cdot}kg^{-1}{\cdot}h^{-1}$. The rest anesthesia protocol was the same for both groups. Electroencephalogram data was recorded before anesthesia induction till the end of surgery. Cognitive function was assessed preoperatively, and at the first, third, fifth, and seventh day postoperatively.

Results: Compared with Group M, Group R had significantly higher intraoperative power spectral density of the frontal alpha band ($P < 0.001$), and significantly lower incidence of postoperative cognitive dysfunction at T_8 and T_9 ($P = 0.031$ and $P = 0.017$, respectively).

Conclusion: Remimazolam can increase frontal brain wave alpha band power spectrum density and improve postoperative cognitive function in older adults undergoing lower extremity fractures surgeries.

Keywords: brain waves, alpha band, benzodiazepines, remimazolam, cognitive dysfunction, elderly, neuropsychological tests

Introduction

Postoperative cognitive dysfunction (POCD) is a common neurological complication following surgery in older adults and has become one of the research hotspots in perioperative medicine in recent years.[1,2] More than 19 million patients ≥65 years old receive anesthesia and surgery each year.[3] Studies have reported that POCD affects 5–55% of older adults after noncardiac surgeries, with even higher incidence observed in those undergoing hip fracture surgeries.[4] The occurrence of POCD can not only hinder patients' recovery but increase the risk of dementia, reduce the quality of life, and even lead to higher mortality rates.[5] Glumac et al[6] highlighted the multifactorial etiology of POCD,

Received: 15 September 2024
Accepted: 26 November 2024
Published: 31 December 2024

encompassing surgery-related, anesthesia-related, and patient-specific risk factors. These complex, interdependent mechanisms underscore the need for targeted anesthetic strategies to mitigate POCD risk.

Recent researches have explored that the expression of low density of electroencephalogram (EEG) alpha band power might be associated with perioperative cognitive dysfunction.[7,8] The reduction of alpha band power can progress to burst suppression, impacting cognitive function, and contributing to the development of POCD.[9]

Remimazolam, an ultra-short-acting benzodiazepine sedative, is known for its rapid onset of action and quick clearance without accumulation. It has been shown to be safe for procedural sedation,[10] as well as for induction and maintenance of general of anesthesia.[11] In older adults undergoing upper gastrointestinal endoscopy, the application of remimazolam produced positive neuropsychiatric functions.[12] A previous animal study demonstrated that, in contrast to midazolam, remimazolam had a lesser negative impact on cognitive function.[13,14] Clinical studies have suggested that remimazolam could potentially reduce the incidence of POCD in older adults,[15,16] possibly through its anti-inflammatory properties.[17] A preclinical study conducted in sheep examined the EEG changes induced by remimazolam and midazolam, revealing that remimazolam elicited a higher magnitude of alpha band power.[18] The above study also noted the absence of burst suppression or isoelectric EEG patterns during remimazolam administration. We hypothesized that remimazolam could improve postoperative cognitive function by augmenting intraoperative frontal alpha band power intraoperatively in older adults. This study was then undertaken to evaluate the effect of remimazolam on intraoperative alpha band activity and postoperative cognitive outcomes in older adults undergoing lower extremity fracture surgeries.

Methods

Study Design and Ethics

The study was a single-center, prospective, randomized, double-blinded, and controlled trial to evaluate the effect of remimazolam and midazolam intraoperative frontal brain wave alpha band activity and postoperative cognitive function in the older adults undergoing lower extremity fractures surgeries. The study was approved by the Ethics Committee of the Affiliated Hospital of Yangzhou University (2020-YKL09-025-3) in accordance with the Declaration of Helsinki and was registered on the ClinicalTrials.gov website (NCT04601350). All patients signed informed consent form.

Participants

Patients older than 65 years old, gender unlimited, and American Society of Anesthesiologists (ASA) physical status of class I to III undergoing lower extremity fracture surgery under general anesthesia were recruited from November 2020 to May 2022. Inclusion criteria were no preoperative cognitive impairment (assessed by the Mini Mental State Examination [MMSE] score: >17 for illiteracy, >20 for primary school, and >24 for middle school and above), and estimated surgery duration ≥1 h. Exclusion criteria included refusal or non-cooperation of patients and family members, inability to understand and answer the questionnaire without help, previous history of allergy to sedative or analgesic drugs, previous history of psychiatric disorders, and long-term use of sedative, analgesic drugs or anti-anxiety drugs. The elimination criteria consisted of serious interference of intraoperative EEG signals, serious circulatory failure during the operation, need to be transferred to ICU for further treatment after surgery, and incomplete follow-up information.

Randomization and Blinding

A computer-generated simple randomization list with 1:1 allocation was created by a researcher who was not involved in the trial process, follow-up, and analysis before the study. For allocation concealment, assignments were placed in sealed opaque envelopes, which were sequentially handed to clinicians after randomization, before entering the operating room. Data were collected and analyzed by two researchers who were blinded to the randomization to minimize bias and achieve allocation concealment. Experienced trial supervisors supervised the trial to ensure integrity of the blinding process and regularly reviewed the experimental data for accuracy and completeness. Patients, surgeons, nurses, anesthesiologists, and outcome observers were blinded to the randomization and drugs administered to the various groups throughout the study period.

Trial Procedure

After patients' admission to the operating room, an intravenous line was established on their non-dominant hand for fluid infusion. All Patients were monitored routinely with electrocardiograph (ECG), heart rate (HR), blood pressure (BP), and oxygen saturation (SpO_2). The raw EEG signals monitoring was conducted using an EEG cap (BM-5010, Greentek Inc., Wuhan, China). Reusable sintered Ag/AgCl electrodes (Greentek Inc., Wuhan, China) were placed at the following positions according to the international 10/20 system: F3, F4, C3, C4, O1, O2, Cz (common reference), and Fp1 (ground). GT20 medical conductive gel (Greentek Inc., Wuhan, China) was injected through each electrode hole using the special syringe to keep the impedance below 10 KΩ. An Arc EEG acquisition system (Cadwell Industries Inc., USA) was connected for information acquisition and analysis.

According to the site of fracture and surgical approach, nerve block was administered under ultrasound guidance with local anesthesia. The nerve block was performed by anesthesiologists those had 1 year of nerve block specialty training to ensure analgesia effect. For general anesthesia induction, in Group R, remimazolam (211125AK, Jiangsu Hengrui Medicine Co., China) 0.01 mg/kg (diluted to 10 mL with normal saline) was intravenously injected with the injection time of 1 min for general anesthesia induction, followed by continuous intravenous infusion of 0.1 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ till the end of surgery; Group M, midazolam 0.05 mg/kg (diluted to 10 mL with normal saline) was intravenously injected with the injection time of 1 min for general anesthesia induction, followed by continuous intravenous infusion of saline 0.1 $mL{\cdot}kg^{-1}{\cdot}h^{-1}$ till the end of surgery. Three minutes later, both groups received propofol 1–1.5 mg/kg, sufentanil 0.2 μg/kg, and rocuronium bromide 0.6 mg/kg. Endotracheal intubation was performed after muscle relaxation. Mechanical ventilation was set with inhaled oxygen concentration of 60%, tidal volume of 6–8 mL/kg, respiratory rate of 12–14 breaths/min, inspiratory/expiratory ratio of 1:1.5 to maintain end-tidal carbon dioxide partial pressure of 35–45 mmHg (1 mmHg=0.133 kPa). Sufentanil was added to an intraoperative total dose of 0.3–0.5 μg/kg. Rocuronium bromide was administered intermittently to maintain muscle relaxation. General anesthesia was maintained with intravenous infusion of propofol 4–10 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$, remifentanil 0.2–0.5 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$, and inhaled sevoflurane 0.7 minimum alveolar concentration. The endotracheal tube was removed when the indication for extubation was reached after surgery finish. All the patients were then transferred to the post-anesthesia care unit (PACU) for further clinical observation.

MAP and HR were recorded immediately before induction of general anesthesia (T_1), after induction of general anesthesia (T_2), and after tracheal intubation (T_3), at the beginning of surgery (T_4), 30 min after the beginning of surgery (T_5), at the end of surgery (T_6), and 30 min after transferring to the PACU (T_7). Blood samples were collected 1 day preoperatively (T_0), the first day postoperatively (T_8), and the third day postoperatively (T_9), and were centrifuged at 3000 rotation/min for 10 min at 4°C for examination of plasma concentrations of IL-6, IL-10, and S100-β using commercial ELISA kit. Postoperative cognitive function was assessed by MMSE at T_0, T_8, T_9, the fifth day post-operatively (T_{10}), and the seventh day postoperatively (T_{11}).

EEG data was gathered from the time point of T_1 to T_6. The EEG spectrogram was visually inspected by an EEG doctor who did not participate in the study procedure to make sure that the analysis windows were free of artifacts. Each EEG recording was analyzed by at least two independent technologists experienced in EEG interpretation, who were also unaware of the grouping criteria. The data was pretreated first based on an EEGlab tool kit applying a standard treatment procedure. First, the raw EEG data was imported into the EEGlab; Second, 1–30 hz bandpass filtering was confirmed; And third, EEG signals with a duration of 3 min with no artifacts were selected for the following analysis. The time-frequency decomposition of EEG data is performed based on Morlet wavelet decomposition. The peak frequency of Morlet wavelet varies linearly from 1 hz to 30 hz (linear equal to 60 parts). The cycle number of the corresponding wavelet changes linearly from 5 to 15 (also linearly divided into 60 parts). Therefore, for each EEG data, we can obtain a 2D time-frequency result matrix of a frequency point * time point. The power spectral density estimation of Welch method can be realized by using pwelch function in Matlab directly. A Hanning window with a length of 2 s was used, and the number of Fourier transform data points was set to 1024. Finally, the average power spectral density of alpha band was calculated in the range of 8–13 hz.

Outcome Measures

The primary outcome of the present study was the average intraoperative power spectral density of the frontal alpha band. Secondary outcomes included the incidence of POCD, vital signs at different time points, intraoperative administration of anesthetics, vasoactive drugs, the incidence of adverse events, including hypotension, intraoperative bradycardia, and postoperative respiratory depression.

POCD was defined as a reduction of MMSE scores more than 2 points of basal value. The fluctuations of hemodynamics were maintained between ±20% of the base value. In instances where the reduction of mean arterial pressure (MAP) surpassed 20% of the baseline, ephedrine or phenylephrine was administered. Additionally, atropine was employed if the heart rate (HR) decrease exceeded 20% of the baseline value.

Sample Size Calculation

PASS 15.0 software (NCSS LLC, Kaysville, Utah) was used to calculate the sample size. According to our preliminary trial, the intraoperative mean power spectral density of alpha band in Group M was (6.32±2.83) dB, and it was expected that the intraoperative mean power spectral density of alpha band in Group R was 20% higher than that in Group M. Based on an alpha error of 0.05 and power of 90% (test for two proportions, two-sided test), it was calculated that at least 25 patients was needed to be included in each group. Considering the possibility of loss to follow-up or consent withdrawals, a minimum of 32 patients were recruited in each group.

Statistical Analysis

IBM SPSS 25.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for data analysis. GraphPad Prism 8.0.2 (GraphPad Inc., Boston, MA, USA) was used for plotting. Continuous data were tested for normality. Normally distributed measures were expressed as mean ± standard deviation. Data with abnormal distribution were presented as median (25th and 75th percentile) and compared using Mann–Whitney *U*-test. Risk ratio (RR), risk difference (RD) and difference were reported with 95% confidence intervals (CIs). For between-group comparisons, a *t*-test was used (variance homogeneity); Welch's analysis of variance was used for variance nonhomogeneity. Comparisons of measures at different time points were performed using repeated measures ANOVA in groups. Categorical data were presented as absolute values and percentages, and compared using Fisher's exact test or chi-squared test. $P<0.05$ was considered a statistically significant difference.

Results

A total of 120 patients were initially screened. Twenty-eight patients did not meet the inclusion criteria and were consequently excluded, while an additional 10 patients chose not to participate. Three patients in Group R and 2 patients in Group M were lost to follow up postoperatively. Three patients in Group R and 4 patients in Group M were eliminated due to improperly fitted EEG electrodes with poor data quality. In the end, A total of 70 patients completed the trial, with 35 cases in each group Figure 1. There were no significant differences between the two groups with regard to demographics and the surgery information Table 1.

The average intraoperative power spectral density of the frontal alpha band of patients in Group R [8.61 (6.95, 10.41)] was significantly higher than that in Group M [5.69 (3.69, 7.69)] ($P < 0.001$). Figures 2 and 3 demonstrated the intraoperative EEG time-frequency analysis maps plotted in one patient in Group M who developed PCOD and one patient in Group R who did not develop POCD, respectively.

Compared with T_0, MMSE score was significantly decreased at T_8 ($P < 0.001$), T_9 ($P < 0.001$) and T_{10} ($P < 0.001$) in Group M, respectively, and at T_8 ($P < 0.001$) and T_9 ($P < 0.001$) in Group R, respectively. Compared with Group M, Group R had significant higher MMSE score at T_8 ($P = 0.044$) and T_9 ($P = 0.046$) Table 2. The incidence of POCD at T_8 and T_9 was significantly lower in Group R than Group M ($P = 0.031$ and $P = 0.017$, respectively) Table 3.

Compared with T_0, IL-6, IL-10, and S100-β were significantly higher at T_8 ($P < 0.001$, $P < 0.001$, and $P = 0.013$ in Group R; $P < 0.001$, $P < 0.001$, and $P = 0.003$ in Group M, respectively) and T_9 ($P < 0.001$, $P < 0.001$, $P = 0.049$ in Group R; $P < 0.001$, $P < 0.001$, $P = 0.001$ in Group M, respectively) in both groups. Compared with Group M, IL-6 at T_8

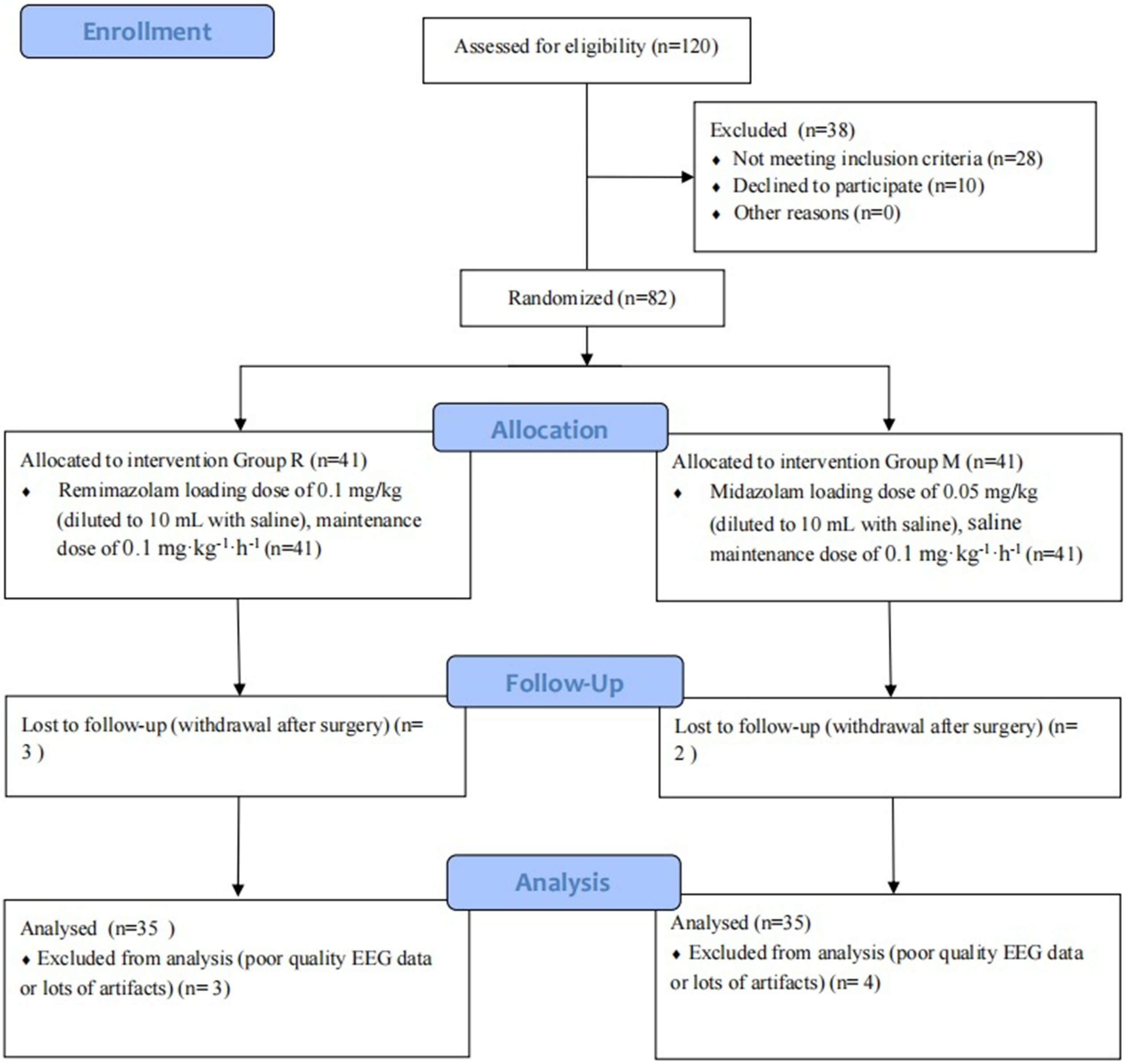

Figure 1 CONSORT diagram of patient recruitment.

(P = 0.004), S100-β at T_8 and T_9 were significantly lower (P = 0.026 and P = 0.022, respectively), and IL-10 was significantly higher at T_8 in Group R (P = 0.004) Figure 4.

There were no statistically significant differences in MAP and HR between the two groups at T_1. Compared with T_1, MAP was significantly decreased at T_3 to T_7 in both groups (P = 0.018, $P < 0.001$, $P < 0.001$, $P < 0.001$, and P = 0.001 in Group R, respectively; P = 0.001, $P < 0.001$, $P < 0.001$, $P < 0.001$, and $P < 0.001$ in Group M, respectively); HR was significantly increased at T_2 (P = 0.002) and T_3 (P = 0.012) in Group R, and significantly decreased at T_4 to T_7 in Group M ($P < 0.001$, $P < 0.001$, $P < 0.001$ and P = 0.001, respectively). Compared with Group M, Group R had significantly higher MAP and lower HR at T_5 and T_6 (P = 0.020, P = 0.022, P = 0.016 and P = 0.007, respectively) Figure 5.

There were no statistically significant differences in the consumption of intraoperative propofol, sufentanil, and remifentanil between the two groups. No statistically significant differences occurred in the incidence of intraoperative bradycardia and the rate of atropine use between the two groups. In Group R, the incidence of hypotension and postoperative respiratory depression were significantly lower than Group M. The intraoperative utilization of ephedrine and phenylephrine were also significantly less in Group R than in Group M (P = 0.046 and P = 0.022, respectively) Table 4.

Table 1 Comparison of the Demographics and Surgery Information Between the Two Groups

	Group R (n=35)	Group M (n=35)	*P*-value
Age (years)	72.23±4.39	71.97±4.88	0.818
Gender (M/F)	17/18	15/20	0.631
BMI (kg/m^2)	22.6±2.5	23.2±2.9	0.401
ASA (I/II/III)	8/23/4	11/22/2	0.559
Educational level (illiterate/primary/middle/high school)	4/15/13/3	5/18/10/2	0.807
Site of fracture (A/B/C)	21/6/9	19/9/6	0.537
Surgical modalities (A'/B'/C')	16/9/10	15/11/9	0.867
Duration of surgery (min)	65 (60,75)	65 (60,75)	0.929
Duration of anesthesia (min)	95 (90,105)	95 (90,105)	0.771
Fluid infusion volume (mL)	1500 (1000,1500)	1500 (1000,1500)	0.764
Estimated blood loss volume (mL)	100 (100,200)	150 (100,200)	0.424
Urine volume (mL)	200 (100,300)	200 (150,250)	0.947
PACU retention time (min)	34 (32,35)	34 (33,35)	0.943

Notes: Data are expressed as mean ± SD, median (P25, P75) or numbers of cases.
Abbreviations: R, Remimazolam; M, Midazolam; BMI, body mass index; ASA, American Society of Anesthesiologists; PACU, post-anesthesia care unit. A, proximal femur fracture; B, distal femur fracture; C, tibiofibular fracture; A', open reduction and internal fixation; B', closed reduction and internal fixation; C', artificial joint replacement.

Discussion

In the present prospective, randomized, double-blind, and controlled clinical trial, participants were randomly assigned to the remimazolam group and midazolam group, we compared the effects of remimazolam on intraoperative frontal brain wave alpha band activity and postoperative cognitive function in older adults undergoing lower extremity fractures surgeries. The results showed that remimazolam application for the induction and maintenance of general anesthesia could improve spectral density of intraoperative frontal brain alpha power and postoperative cognitive function in older adults undergoing lower limb fracture surgery compared with midazolam.

POCD is one of the severe complications during the perioperative period, influenced by factors such as advanced age, preoperative cardiovascular and cerebrovascular diseases, surgical trauma stimulation, residual anesthetic drugs, and intraoperative brain electrical activity suppression.[19] The impact of intraoperative brain electrical activity suppression on POCD has garnered attention from researchers in recent years.[20] Older adults often exhibit reduced brain capacity due to

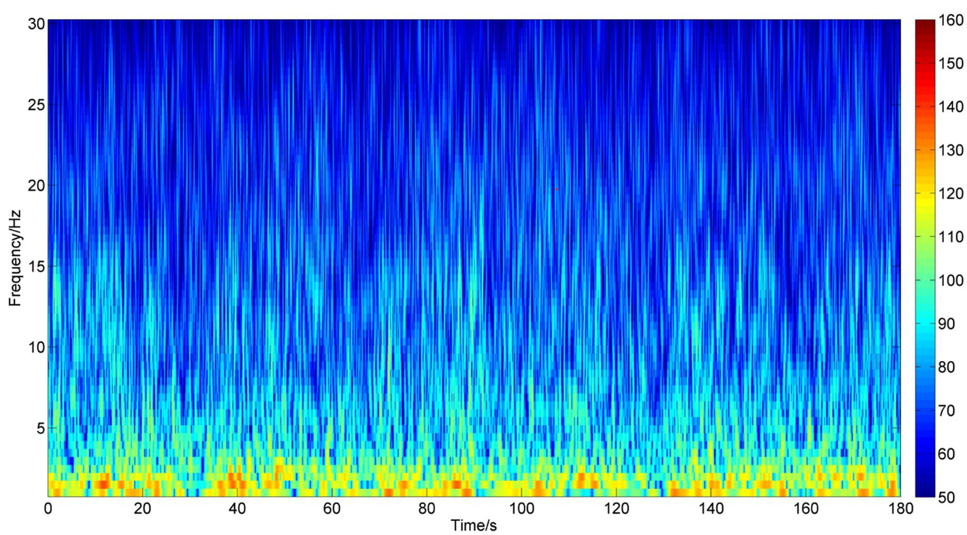

Figure 2 Intraoperative frontal EEG time-frequency analysis of a patient who developed POCD in Group M.

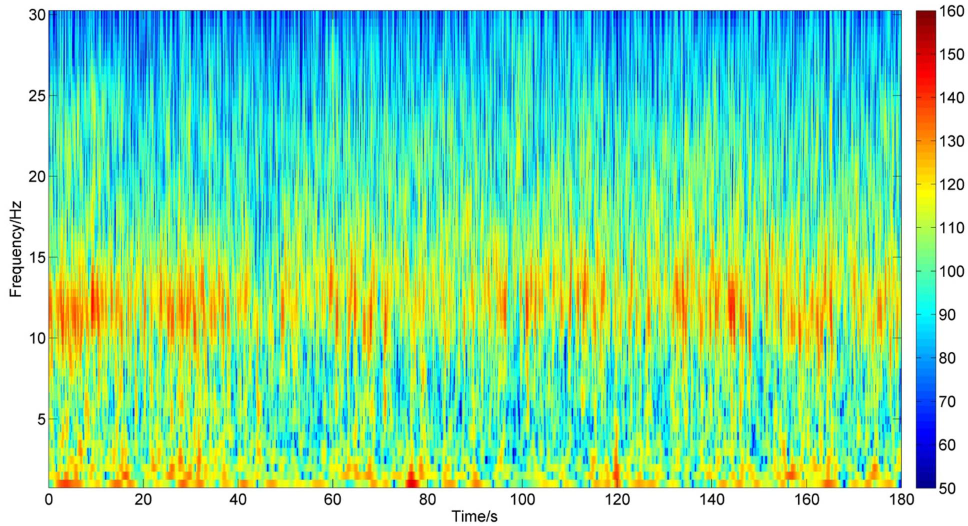

Figure 3 Intraoperative frontal EEG time-frequency analysis of a patient without POCD in Group R.

neurodegenerative changes, leading to a higher POCD prevalence.[21] These older adults' brains are commonly termed as "vulnerable brain".[22,23]

Recent studies indicated the importance of utilizing EEG for routine monitoring during intraoperative period to mitigate complications arising from inadequate or excessive anesthesia.[24] The EEG can capture oscillations in brain systems and circuits induced by general anesthetics and sedatives. Human brain waves are categorized into Alpha, Beta,

Table 2 Comparison of MMSE Score at Each Time Point Between the Two Groups

	Group R (n=35)	Group M (n=35)	*P*-value
T_0	26.2±2.1	26.4±1.6	0.612
T_8	25.5±2.3	24.3±2.3	0.044
T_9	25.6±2.3	24.5±2.1	0.046
T_{10}	26.0±2.2	25.8±1.6	0.714
T_{11}	26.3±2.3	26.3±1.7	0.953
$P_{T0\text{-}8}$	<0.001	<0.001	
$P_{T0\text{-}9}$	<0.001	<0.001	
$P_{T0\text{-}10}$	0.110	<0.001	
$P_{T0\text{-}11}$	0.136	0.539	

Note: Data are presented as mean±SD.
Abbreviations: T_0, 1 day preoperatively; T_8, the first day postoperatively; T_9, the third day postoperatively; T_{10}, the fifth day postoperatively; T_{11}, the seventh day postoperatively.

Table 3 Comparison of the Incidence of POCD Between the Two Groups

	Group R (n=35)	Group M (n=35)	RR, Difference (95% CI)	RD, Difference (95% CI)	*P*-value
T_8	3 (8.6%)	10 (28.6%)	0.300 (0.090 to 0.998)	−20 (−37.6 to −2.4)	0.031
T_9	3 (8.6%)	11 (31.4%)	0.273 (0.083 to 0.894)	−22.9 (−40.8 to −4.9)	0.017
T_{10}	1 (2.8%)	3 (8.6%)	0.333 (0.036 to 3.051)	−5.7 (−16.5 to −5.1)	0.607
T_{11}	0 (0)	2 (5.7%)	0	−5.7 (−13.4 to −2.0)	0.473

Note: Data are presented as numbers of patients (%).
Abbreviations: T_8, the first day postoperatively; T_9, the third day postoperatively; T_{10}, the fifth day postoperatively; T_{11}, the seventh day postoperatively; RR, risk ratio; RD, risk difference.

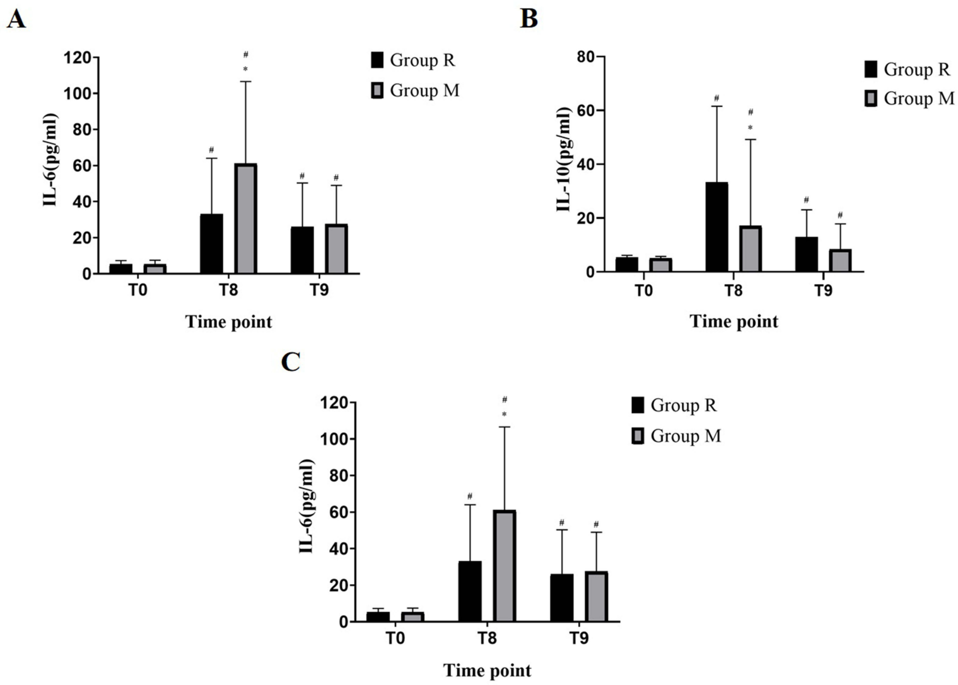

Figure 4 Changes of plasma concentrations of IL-6, IL-10, and S100-β in the two groups. Plasma concentrations of IL-6, IL-10, and S100-β at different time points in the two groups; plasma concentrations of IL-6 (**A**); plasma concentrations of IL-10 (**B**); plasma concentrations of S100-β (**C**).
Notes: *Compared with Group M, $P < 0.05$; #Compared with T_0, $P < 0.05$.
Abbreviations: T_0, one day preoperatively; T_8, the first day postoperatively; T_9, the third day postoperatively.

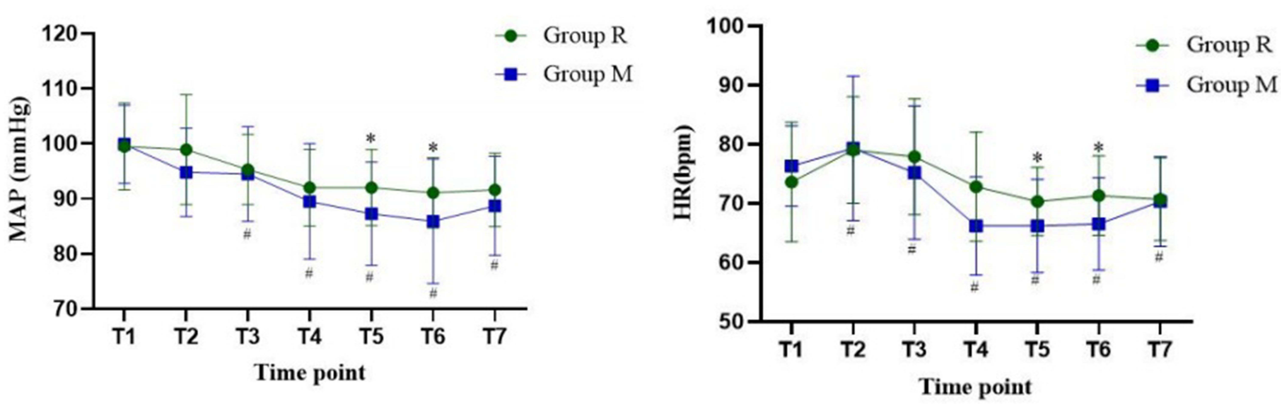

Figure 5 Comparison of MAP and HR between the two groups.
Notes: *Compared with Group M, $P < 0.05$; #Compared with T_0, $P < 0.05$.
Abbreviations: T_1, immediately before induction of general anesthesia; T_2, immediately after induction of general anesthesia; T_3, immediately after tracheal intubation; T_4, at the beginning of surgery; T_5, 30 min after the beginning of surgery; T_6, at the end of surgery; T_7, 30 min after transferring to the PACU.

Delta, Gamma, and Theta bands based on the frequency range of EEG signals. The vulnerable brain displays variances in anatomy and physiology compared to younger brains, leading to corresponding changes in brain waves. A key alteration is the reduction in power across all frequency bands, particularly a significant decrease in the peak frequency of alpha band. Decreased alpha power during general anesthesia serves as a crucial indicator of "vulnerable brain", with patients exhibiting this characteristic being more prone to intraoperative burst suppression and an increased incidence of POCD.[25] The potential pathophysiological mechanism may involve decreased central nervous synaptic density, diminished neurotransmitter synthesis in hippocampal dentate neurons or cortical neurons, and reduced postsynaptic currents.[1] Gaskell et al[26] suggested in their study that enhancing the alpha band power during anesthesia might improve

Table 4 Comparisons of the Consumption of Anesthetics and Vasoactive Agents, and Adverse Events Between the Two Groups

	Group R (n=35)	Group M (n=35)	*P*-value
Propofol dosage (mg)	404.8±56.7	409.9±56.3	0.706
Sufentanil dosage (mg)	20 (20,20)	20 (20,20)	0.100
Remifentanil dosage (mg)	0.42±0.10	0.43±0.09	0.701
Bradycardia (n, %)	5 (14.3%)	11 (14.3%)	0.088
Atropine (n, %)	3 (8.6%)	3 (8.6%)	0.101
Ephedrine (n, %)	3 (8.6%)	3 (8.6%)	0.046
Phenylephrine (n, %)	3 (8.6%)	3 (8.6%)	0.022
Postoperative respiratory depression (n, %)	3 (8.6%)	10 (28.6%)	0.011
Hypotension (n, %)	2 (5.7%)	10 (28.6%)	0.031

Note: Data are presented as mean±SD, median (P25, P75) or numbers of patients (%).

postoperative neurocognitive function. In Shao et al's[3] research, the reduction in anesthesia-induced frontal alpha power correlated with increased burst suppression. The authors explored that during propofol bolus infusion, every one decibel decrease in alpha band power led to a 1.33-fold rise in burst suppression. The increased alpha oscillations could function as a neurophysiological biomarker for brain protection. Therefore, maintaining or enhancing the EEG alpha band power intraoperatively might reduce the occurrence of burst suppression, mitigate perioperative damage to "vulnerable brain", and consequently lower the incidence of POCD.

Remimazolam, a new type of water-soluble benzodiazepine sedative, acts on the GABAA receptors. It features an easily metabolized ester structure, enables organ-independent metabolism similar to remifentanil, and not susceptible to accumulate after prolonged infusion.[18] Rapid hydrolysis by tissue esterases converts it into the inactive carboxylic acid metabolite CNS 7054, which also binds to GABAA receptors but with an affinity only 1/400 of remimazolam.[27] Previous observational research conducted on healthy male volunteers aged 18–40 years with remimazolam injection showed a transient increase in frontal EEG beta activity, followed by a significant increase in alpha activity.[18] In our current study, we found that remimazolam used for general anesthesia induction and maintenance led to a substantial augmentation in the spectral density of intraoperative EEG frontal alpha band power, along with a reduced incidence of POCD compared to the group administered midazolam as the controlled benzodiazepine sedative. The protective impact of remimazolam on postoperative cognitive function might be related to its enhancement of alpha band activity. Furthermore, remimazolam maintained stable hemodynamics, potentially benefiting blood supply to the central nervous system.

The MMSE stands as one of the most influential and globally utilized tools for screening cognitive impairment.[28,29] It comprises 11 items covering time and place orientation, immediate memory, attention and calculation, short-term memory, language, and visuospatial abilities, demonstrating high reliability. In this study, we evaluated patients' cognitive function and determined the incidence of POCD based on the MMSE scores. S100-β, a marker protein released by neuroglial cells, correlates with reduced brain function.[30,31] Elevated blood levels of S100-β indicate neuroglial cell damage and can predict the onset of POCD. Increased plasma IL-6 levels are also closely tied to POCD.[32] IL-10, an anti-inflammatory cytokine secreted by M2 macrophages, hinders inflammatory cell activation, migration, and adhesion, as well as the production of inflammatory factors.[33] In this current study, Group R exhibited postoperative higher level of IL-10, while lower levels of S100-β and IL-6 than Group M. The protective effects of remimazolam on postoperative cognitive function might also be linked to its anti-inflammatory properties.

The key strength of this study lies in our thorough monitoring of EEG changes during remimazolam use. By tracking the spectral density of different EEG bands, including the alpha band, we can better understand how remimazolam protects postoperative cognitive function. Traditionally, the brain wave monitoring during anesthesia has primarily focus on assessing anesthesia depth through a single numerical value ranging from 0 and 100. Little has been made for exploring the potential mechanisms underlying the waveforms. Our research indicates that EEG may provide valuable

 https://doi.org/10.2147/CIA.S496437

insights into intraoperative brain function. Variations in EEG activity during general anesthesia could be considered as a characteristic of the underlying brain pathophysiology.

However, this study has certain limitations. Firstly, it solely focused on older adults undergoing lower limb fracture surgery. Further research is needed to investigate if remimazolam offers cognitive protection in patients undergoing different surgical procedures. Secondly, due to the EEG signals instability during the short period from patients' entry into the operating room to general anesthesia induction, obtaining preoperative EEG data was challenging, hindering the comparison of frontal alpha power levels between the two groups. Thirdly, we performed cognitive assessment only based on the MMSE in this study, which, although practical, may not capture detailed cognitive changes. A broader neuropsychological test battery should be used in future studies for a more comprehensive evaluation of postoperative cognitive function. Finally, due to the single-center trial with a small sample size, large multicenter studies are essential to delve into the specific mechanism of remimazolam's impact on brainwaves and postoperative cognitive function.

Conclusion

Remimazolam with a loading dose of 0.1 mg/kg and a maintenance dose of 0.1 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ can increase frontal brain wave alpha band power spectrum density and potentially improve postoperative cognitive function in older adults undergoing lower extremity fractures surgeries.

Data Sharing Statement

All data generated or analyzed during this study were included in the published article. Further inquiries about the datasets can be directed to the corresponding author on reasonable request.

Acknowledgments

The authors sincerely thank the nurses and the orthopedists for their support and help.

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR.

Funding

This work was supported by General Project of Jiangsu Province Traditional Chinese Medicine Technology Development (MS2022151); Social Development Project of Yangzhou Science and Technology Plan (YZ2022108).

Disclosure

The authors have no competing interests in this work.

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