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Effects of adjunctive esketamine on depression in elderly patients undergoing hip fracture surgery: a randomized controlled trial

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Abstract

Background Depression is a prevalent perioperative psychiatric complication among elderly hip fracture patients. Esketamine has rapid and robust antidepressant effects. However, it is unknown whether it can alleviate depressive symptoms in elderly patients who undergo hip fracture surgery. This study aimed to explore whether the adjunctive esketamine in patient-controlled intravenous analgesia (PCIA) could improve depressive symptoms in elderly patients undergoing hip fracture surgery.

Methods A single-center, prospective, double-blind and randomized controlled clinical trial was carried out from July 2022 to August 2023 at the Wenzhou People's Hospital among 90 patients, aged ≥ 65 years with hip fracture undergoing elective surgery. Participants were randomly allocated to either the esketamine group (group S) or the control group (group C). In Group S, patients were administered 0.5 mg/kg of esketamine as a PCIA adjuvant for 48 h, while the control group received saline. The primary outcome was the assessment of depressive symptoms using the Geriatric Depression Scale-15 (GDS-15) on postoperative day 2. The secondary outcomes were assessments of depressive symptoms on postoperative day 7 and postoperative day 30, serum levels of brain-derived neurotrophic factor (BDNF) and 5-hydroxytryptamine (5-HT), postoperative pain intensity, the number of effective PCIA presses, sufentanil consumption, and adverse events.

Results The prevalence and GDS-15 scores of depression were significantly lower in group S on postoperative day 2 (28.6% vs. 53.5%; 3.5 ± 1.8 vs. 4.3 ± 1.7, $P < 0.05$). In group S, the number of effective PCIA presses was significantly lower on postoperative day 2 than that in group C [2(1–4) vs. 1(0–2), $P<0.05$]. Higher levels of BDNF (23.8 ± 1.7 ng/mL vs. 25.3 ± 2.0 ng/mL, $P < 0.05$) and 5-HT (219.5 ± 19.5 ng/mL vs. 217.0 ± 22.2 ng/mL, $P < 0.05$) in the blood were observed on postoperative day 2 in group S.

Conclusion In elderly patients aged ≥ 65 years undergoing hip fracture surgery, the administration of adjunctive esketamine in PCIA could improve depressive symptoms and increase levels of BDNF and 5-HT in the blood.

Trial registration Chinese Clinical Trial Registry, ChiCTR2200061956 (Date: 13/07/2022).

Keywords Depression, Esketamine, Elderly patients, Hip fracture

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Background

Hip fracture is viewed as a severe injury for elderly people, often with high morbidity, disability, and mortality rates [1]. The incidence of hip fractures increases rapidly with age in the elderly [2]. In urban China, the number of hip fractures among people aged 55 years and older rose approximately fourfold between 2012 and 2016, as the size of the aging population rapidly increased [3]. The aging population is leading to an increase in hip fractures, which is now a concern for public health.

Depression, as a major perioperative psychiatric complication of hip fracture, is also a risk factor that impacts the prognosis of hip fractures [4, 5]. In the short term, depression could increase the risk of infection, delirium, and reoperation, while in the long term, depression is associated with incomplete functional recovery, cognitive disorders, and mortality [6–8]. In the perioperative period, more than 50% of hip fracture patients suffer from depression due to pain, surgery, anesthesia, and restricted activity [9–11]. Hence, a straightforward and efficient method is urgently required to address perioperative depression through treatment and prevention.

Esketamine, a new type of N-methyl-D-aspartic acid (NMDA) receptor blocker, shows stronger pain-relieving and antidepressant properties compared to ketamine [12]. Esketamine nasal spray is the only form of rapid antidepressant to have been approved by the FDA for marketing [13]. Several studies have shown that esketamine offers strong antidepressant benefits for patients undergoing breast cancer, cesarean sections, and orthopedic surgery [14–16]. The antidepressant effect of esketamine in elderly hip fracture patients with depressive symptoms remains uncertain. Therefore, we carried out this randomized controlled trial to investigate whether esketamine could enhance depressive symptoms in elderly individuals undergoing hip fracture surgery when utilized as a supplement in patient-controlled intravenous pain analgesia (PCIA).

Methods

Design

We conducted this single-center, prospective, double-blind and randomized controlled clinical trial at Wenzhou People's Hospital. This study was funded by the Chinese Red Cross Foundation Medical Empowerment Public Welfare Special Fund (CRCF-YXFN-202201002) and Basic Research Project of Wenzhou City (Y20190114/ Y20220218). This study was approved by the Ethics Committee of the Wenzhou People's Hospital (No. KY-2022-029). We registered this trial in the Chinese Clinical Trials Registry (No. ChiCTR2200061956). This study adheres to the CONSORT guidelines (Supplementary 1).

Participants

For this study, we enrolled individuals aged 65 and above undergoing elective hip fracture surgery. Patients were excluded from the trial based on the following criteria: (1) polytrauma; (2) contraindications to anesthesia or surgery; (3) inability to communicate effectively due to coma, cognitive impairment, and other disorders; (4) multiple surgeries during hospitalization; (5) contraindications to esketamine; (6) participation in another trial in the last 3 months. As a measure of cognitive impairment, we adjusted the Chinese version of Mini-Mental State Examination (MMSE) score for the patient's educational level (24 scores for less than postsecondary education, 23 scores for less than secondary education, 20 scores for less than primary education) as previous studies [17, 18].

Randomization and blinding

We randomly assigned patients to groups S and C using a random number table generated by www.random.org. The group information were encased in opaque envelopes, which were opened and prepared with esketamine or 0.9% saline for PCIA by a nurse not involved in the follow-up assessment. Researchers and participants were blinded to the randomization assignment.

Anesthetic techniques and intervention

The anesthesia methods employed in this study included combined lumbar-rigid anesthesia and fascia iliaca compartment block. Upon admission, intravenous access was established, and monitoring of the heart rate, blood pressure, electrocardiogram, and oxygen saturation was also performed. A total of 30 ml of 0.375% levobupivacaine was administered into the iliac fascial space on the affected side under ultrasound guidance. As the affected side faces upward, the puncture procedure was performed at the gap between L2 and L3 or L3 and L4. The cerebrospinal fluid reflux was monitored, and the ropivacaine was diluted into a 0.5% isotonic solution. A slow injection of 2 ml of the solution was administered into the cephalic end, followed by the removal of the lumbar anesthesia needle. Subsequently, a 3–5 cm epidural catheter was placed into the cephalic end of the epidural. Additional injections of 0.5% ropivacaine were administered if the anesthesia level was below T10 during surgery. Intraoperative vasoactive drugs were used to maintain the patient's mean arterial pressure within ± 10% of baseline.

The PCIA was performed in both the groups using different analgesic formulations. Specifically, the group C

received sufentanil at a dosage of 2 μg/kg and tropansetron at a dosage of 5 mg, while the group S received esketamine (Hengrui Medicne, China, H20247040) at a dosage of 0.5 mg/kg, sufentanil (Renfu Medicne, China, H20237165) at a dosage of 2 μg/kg and tropansetron at a dosage of 5 mg. They were all diluted in saline to 100 ml. PCIA was performed for 48 h at a 1.5 mL/h background dose, 1.5 mL/h single dose, and 15 min locking time.

Outcome measure

Outcomes were measured by trained anesthesiologists, all of whom were unaware of the grouping of participants. We assessed depression using the geriatric depression scale (GDS-15) on preoperative 1 day, and on postoperative days 2, 7 and 30. The primary outcomes were the GDS-15 scores and the prevalence of depression on postoperative day 2. The GDS-15 is a well-validated test for the evaluation of depression symptoms in the elderly, which has a total of 15 dichotomous items with a possible range of 0 to 15 as previous studies [19, 20]. Depression was defined as the GDS-15 $\geq$ 5 [21].

Secondary outcomes in the trial included the assessment of depression symptoms on postoperative days 7 and 30, the worst pain score, serum levels of BDNF and 5-HT, times of effective presses, consumption of sufentanil, and adverse events. The visual analog scale (VAS), which ranged from 0 to 10, was used to assess the pain score over after surgery. The adverse events in this trial were nausea and vomiting, dizziness, hallucinations and nightmares. Serum was collected from patients one day before and 2 days after surgery. Blood was centrifuged at 1000 g for 10 min at 4 ℃ to obtain serum and stored at -80 ℃. We measured BDNF and 5-HT serum levels using enzyme-linked immunosorbent assays (ELISA).

Sample size calculation

Depression is reported to be prevalent among older patients scheduled for hip fracture surgery at an estimated 58% [11]. We hypothesized that the prevalence of depression was expected to decrease to 29% in group S. The determination of the sample size was conducted using powerandsamplesize.com, with a two-sided $\alpha = 0.05$ and a statistical power of 0.8. The calculations indicated that a minimum of 40 patients should be allocated to each group. Considering a 10% attrition, we decided to enroll a total of 90 patients for the trial.

Statistical analysis

We carried out our statistical analysis using SPSS version 26.0 (SPSS Inc., USA). Categorical data were shown as frequencies or percentages and analyzed using Pearson's $\chi 2$ tests or Fisher's exact test. Odds Ratio (OR) with 95% Confidence Interval (CI) were calculated using the binary logistic regression. Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed continuous variables were presented as mean ± standard deviation (SD), while non-normally distributed variables were presented as median interquartile range (IQR). Normally distributed data were tested using a T-test, while non-normally distributed data were tested using a Mann–Whitney U test. Mean or median differences were reported with 95% CIs. Repeated measure analysis of variance was used to test the repeated data. Line correlation were tested using a Person's test. All statistical tests were two-sided and considered significant at a *P*-value less than 0.05.

Results

Demographics

The procedures for patients in the trial are detailed in Fig. 1. Recruitment started in July 2022 and ended in August 2023 at the Wenzhou People's Hospital. A total of 106 patients were screened for eligibility, and 90 consenting participants were randomly assigned to either the esketamine or control groups. The primary outcome and biomarker data for 43 patients in group C and 42 patients in group S were available for analysis. Finally, 2 participants in group C and 1 participants in group S were lost to follow-up on postoperative day 30.

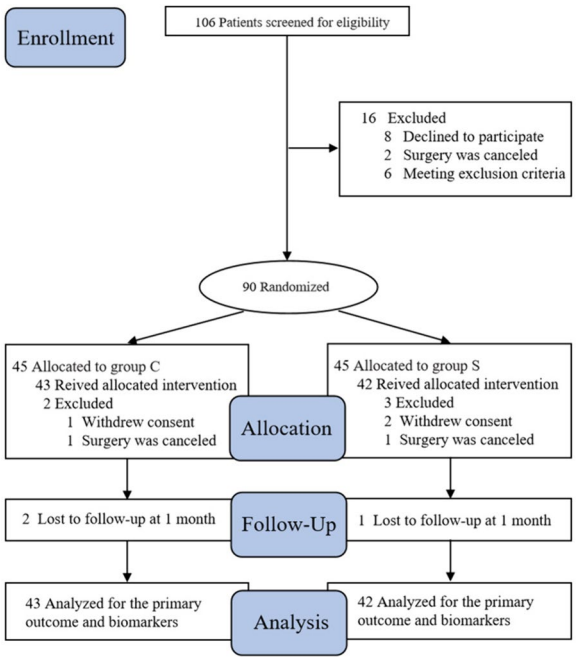

Fig. 1 CONSORT flow diagram illustrating the study design and participant progression

Table 1 Demographic and baseline clinical characteristics

Variables	C($n=43$)	S($n=42$)	*P*
Age, median (IQR), year	74(67-84.5)	76.5(71–85)	0.340
Sex, n (%)			0.063
Men	13(30.3)	21(50.0)	
Women	30(69.8)	21(50.0)	
BMI, mean ± SD, kg/m^2	22.3 ± 3.0	22.7 ± 4.4	0.629
Level of education, n (%)			0.662
< Elementary school	23(53.5)	23(54.8)	
Elementary school	11(25.6)	14(33.3)	
≧Secondary school	9(20.9)	5(11.9)	
ASA physical status, n (%)			0.509
I,	7(16.3)	6(14.3)	
II	33(76.7)	30(71.4)	
III	3(7.0)	6(14.3)	
Comorbidity, n (%)			
Diabetes	5(11.6)	7(16.7)	0.505
Cardiovascular diseases	25(58.1)	27(64.3)	0.561
Respiratory diseases	14(32.6)	13(31.0)	0.874
Nervous Diseases	10(23.3)	10(23.8)	0.952
Type of fracture, n (%)			0.942
Femoral neck	25(58.1)	23(54.8)	
Intertrochanteric	16(37.2)	16(38.1)	
Subtrochanteric	2(4.7)	3(7.1)	
Duration of surgery, median (IQR), minute	109(82–135)	109(85–128)	0.735
MMSE, mean ± SD	22.9 ± 1.8	22.9 ± 1.9	0.904
Duration of hospitalization, mean ± SD, days	12.5 ± 3.0	12.8 ± 3.8	0.667
GDS-15, mean ± SD	4.6 ± 2.0	4.6 ± 1.8	0.927
BDNF, mean ± SD, ng/mL	25.2 ± 1.9	24.9 ± 1.9	0.484
5-HT, mean ± SD, ng/mL	219.5 ± 19.5	217.0 ± 22.2	0.593

Abbreviations: *ASA* American Society of Anesthesiologists, *BMI* Body mass index

There was a good balance in the demographic and clinical characteristics of participants across groups, with no significant differences (Table 1).

Prevalence and GDS-15 scores of depression

The outcomes of the assessments of depression are shown in Table 2. Before the operation, there were no notable differences in the GDS-15 scores of depression among the two groups ($P=0.927$). However, on the second day after surgery, group S exhibited notably lower prevalence of depression and GDS-15 scores compared to group C, with rates of respectively (28.6% vs. 53.5%, $P=0.028$; 3.7 ± 1.63 vs. 4.7 ± 1.62, $P=0.07$, Table 2). While there was no significant difference in prevalence, group S had significantly lower GDS-15 scores on postoperative day 7 compared to group C. (3.5 ± 1.8 vs. 4.3 ± 1.7, $P=0.035$). Repeated measures ANOVA showed significant differences in GDS-15 scores between groups ($F=8.303$, $P=0.005$, $\eta2=0.095$) and time points ($F=8.302$, $P=0.005$, $\eta2=0.095$), while there was no significant interaction in GDS-15 scores between groups and time ($F=0.063$, $P=0.803$, $\eta2=0.001$).

Table 2 Prevalence and GDS-15 scores of depression

Variables	C($n=43$)	S($n=42$)	OR/Mean Difference (95%CI)[a]	*P*
Postoperative day 2				
GDS-15, mean ± SD	4.7 ± 1.6	3.7 ± 1.6	-0.98(-1.69, -0.28)	0.007
Depression, n (%)	23(53.5)	12(28.6)	0.40(0.16, 0.95)	0.020
Postoperative day 7				
GDS-15, mean ± SD	4.3 ± 1.7	3.5 ± 1.8	-0.83(-1.59, -0.06)	0.035
Depression, n (%)	21(48.8)	15(35.7)	0.58(0.24, 1.39)	0.221
Postoperative day 30	C($n=41$)	S($n=41$)		
GDS-15, mean ± SD	3.3 ± 1.6	3.4 ± 1.5	0.10(-0.59, 0.79)	0.779
Depression, n (%)	9(22.0)	10(24.4)	1.15(0.41, 3.20)	0.794

[a] OR(95%CI) applies to the variable Depression, while Mean Difference(95%CI) applies to GDS-15

Analgesic effects

We did not observe significant differences in the pain score (Postoperative day 1, $P=0.323$; Postoperative day 2, $P=0.110$) and sufentanil consumption ($P=0.979$) between the two groups. However, the number of effective PCIA presses were significantly lower in the group S compared to that in the group C ($P < 0.05$, Table 3)

Biomarker

Preoperatively, there was no significant difference in the serum levels of BNDF ($P=0.484$) and 5-HT ($P=0.593$) between the two groups. The levels of BDNF and 5-HT in the serum were notably elevated in group S compared to group C ($P < 0.05$, Table 4). In addition, GDS-15 scores were negatively correlated with serum BDNF and 5-HT levels (Fig. 2).

Adverse events

There was no significant difference in the occurrence of adverse events, including nausea, vomiting, dizziness, hallucinations, nightmares, and pruritus (Table 5).

Discussion

In elderly patients with hip fracture, the results from this randomized controlled trial suggested that adjunctive esketamine in PCIA could improve depressive symptoms

Table 3 Analgesic effects

Variables	C(*n* = 43)	S(*n* = 42)	Mean/Median Difference (95%CI)[a]	*P*
VAS, median (IQR)				
Postoperative day 1	2(1–3)	2(1–3)	0(-1, 0)	0.323
Postoperative day 2	2(1–3)	1(0.75-2)	0(-1, 0)	0.110
Effective press, median (IQR)	2(1–4)	1(0–2)	-1(-2, -1)	<0.001
Sufentanil consumption, mean ± SD, μg	89.7 ± 15.9	89.9 ± 17.9	0.10(-7.21, 7.40)	0.979

[a] Mean Difference(95%CI) applies to the variable Sufentanil consumption and Median Difference(95%CI) applies to VAS and Effective press

Table 4 Serum levels of BNDF and 5-HT on postoperative day 2

Variables	C(*n* = 43)	S(*n* = 42)	Mean Difference(95%CI)	*P*
BDNF, mean ± SD, ng/mL	23.8 ± 1.7	25.3 ± 2.0	1.41(0.61, 2.20)	0.001
5-HT, mean ± SD, ng/mL	206.1 ± 19.3	239.3 ± 24.2	33.24(23.81, 42.67)	<0.001

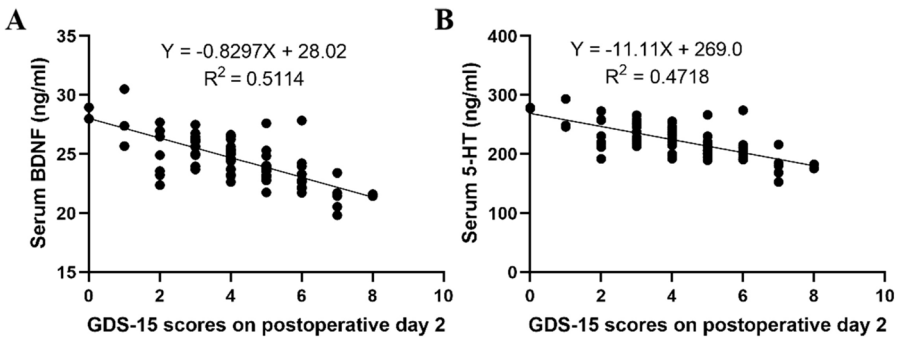

Fig. 2 Serum levels of BDNF and 5-HT. **A** Correlation between GDS-15 and serum BDNF; **B** Correlation between GDS-15 and serum 5-HT

Table 5 Adverse events

Variables	C(*n* = 43)	S(*n* = 42)	OR(95%CI)	*P*
Nausea and vomiting, n (%)	7(16.3)	6(14.3)	0.86(0.26, 2.80)	0.799
Hallucinationsn, n (%)	3(7.0)	2(4.8)	0.67(0.11, 4.21)	0.664
Dizziness, n (%)	3(7.0)	5(11.9)	1.80(0.40, 8.07)	0.684
Nightmares, n (%)	5(11.9)	6(14.3)	1.27(0.36, 4.52)	0.715
Pruritus, n (%)	5(11.9)	6(14.3)	1.27(0.36, 4.52)	0.715

within a week after surgery and elevate serum levels of BDNF and 5-HT.

Depression has long been recognized as a predictor of poor hip fracture prognosis. Although some studies have suggested that poor prognosis due to depression is primarily related to accompanying frailty, another study has shown that early psychological intervention in hip fracture patients with GDS-15 scores ≥ 5 may still benefit patients and reduce the risk of poor recovery [4, 22].

The administration of esketamine is an effective intervention in the perioperative period that improves patients' depressive symptoms. The onset time of the antidepressant effect in conventional 5-HT reuptake inhibitors is typically approximately 45 days, whereas subanesthetic doses of ketamine act rapidly and robustly to reduce depression within 45 minutes, with effects lasting for three days or more [23].

As the dextro isomer of ketamine, esketamine has more potent antidepressant and analgesic effects. Singh et al. [24] demonstrated that administering a single dose of either 0.2 mg/kg or 0.4 mg/kg of esketamine intravenously resulted in a quick and strong antidepressant response. However, this effect was accompanied by adverse events including headache, nausea, and dissociation. Compared with a single intravenous injection, esketamine as an adjuvant in PCIA both improves safety and ensures sufficient effectiveness for antidepressant. Min et al. [15] demonstrated that a dosage of 2.5 mg/kg of esketamine in PCIA conducted an effective and safe antidepressant effect in elderly orthopedic surgery

patients. Yu et al. [25] demonstrated that a dosage of 50 mg of esketamine in PCIA effectively decreased the incidence of depression after cesarean section without an increased incidence of side effects. Han et al. [26] showed that only 0.5 mg/kg of esketamine as an adjuvant combined with sufentanil in PCIA can provide effective antidepressant and analgesic effects. In our study, although there were no significant differences in depressive symptoms between the two groups in the long term, 0.5mg/kg of esketamine as an adjuvant in PCIA definitely improved depression symptoms in hip fracture patients within 7 days after surgery.

There are many possible mechanisms by which esketamine could have improved depression. Multiple research studies suggest that the mood-enhancing effects of esketamine could be due to its indirect stimulation of AMPA receptors, resulting in the release of BDNF [27]. 5-HT deficiency is one of the key hypotheses for the pathogenesis of depression. Several studies have shown that serum levels of 5-HT and BDNF are significantly decreased in both depressed animals and depressed patients [28–30]. Jiang M et al. [31] demonstrated a negative correlation between postoperative serum BDNF levels and the severity of depression in patients who underwent orthopedic surgery. Additionally, Liu et al. [32] observed that in breast cancer patients, pretreatment with esketamine effectively reduced the incidence of postoperative depression, while also elevating levels of BDNF and 5-HT in the blood. In this trial, we also observed that esketamine raised levels of BDNF and 5-HT in hip fracture patients after surgery.

Pain and depression frequently co-occur, with depression potentially exacerbating pain sensitivity and pain potentially causing mood disorders. Numerous research studies have indicated that administering ketamine or esketamine during surgery can effectively reduce pain sensitivity and decrease the need for opioid medications [33]. Brinck et al. [34] showed that esketamine in PCIA reduced postoperative oxycodone dosage in patients that underwent lumbar fusion surgery. It has been reported that esketamine also can alleviate postoperative pain and reduce opioid consumption in patients undergoing thoracic surgery [35]. Wang et al. [36] showed that esketamine combined with sufentanil in PCIA could reduce postoperative pain after a cesarean section and decrease the number of effective presses of PCIA and sufentanil consumption. In our trial, esketamine did not improve VAS scores or sufentanil consumption, but it did reduce the number of effective presses. In addition, the administration of esketamine did not result in a significant increase in the incidence of associated adverse events.

The focus of our study was to investigate the effects of esketamine on depression in hip fracture patients after surgery. We also detected biomarkers of depression such as BDNF and 5-HT in order to confirm stable results. Nevertheless, our trial has some limitations. First, the rehabilitation of hip fractures is a long process, but we only assessed patients' depression in the short term. Second, we only detected biomarkers preoperatively and 2 days postoperatively, and these data do not reflect the depression of patients at postoperative day 7. Third, we only assessed psychiatric complications associated with depression, and did not explore adverse events associated with depressive symptoms as a risk factor, such as delirium, postoperative cognitive dysfunction, and poor recovery.

Conclusions

The administration of adjunctive esketamine in PCIA could improve depression and increase serum levels of BDNF and 5-HT in elderly patients aged ≥ 65 years who have undergone hip fracture surgery.

Abbreviations

ASA	American Society of Anesthesiologists classifcation
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolio propionate
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CI	Confidence Interval
GDS-15	Geriatric Depression Scale-15
IQR	Interquartile range
5-HT	5-Hydroxytryptamine
MMSE	Mini-mental state examination
NMDA	N-methyl-D-aspartic acid
OR	Odds Ratio
PCIA	Patient-controlled intravenous analgesia
SD	Standard deviation
VAS	Visual analog scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02733-0.

Supplementary Material 1

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Additional information

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 (www.parinc.com).

Authors' contributions

Juncheng Xiong presented the Conceptualization; Jiajing Cai design this trial; Jiajing Cai get fund; Zhanghuang Chi prepared esketamine or saline; Ziyuan Jin data collection and analysis; Jiajing Cai wrote the main manuscript text; Juncheng Xiong edited the manuscript; All author reviewed the final manuscript.

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Availability of data and materials
Data and materials are not publicly available, but are available to corresponding or first authors upon reasonable request.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Wenzhou People's Hospital (No. KY-2022-029). Informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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