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# Effect of esketamine on serum neurotransmitters in patients with postpartum depression: a randomized controlled trial

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## Abstract

**Background** The development of postpartum depression has been linked to fluctuations in the levels of neurotransmitters in the human body, such as 5-hydroxytryptamine (5-HT), dopamine (DA), noradrenaline (Norepinephrine, NE), and brain derived neurotrophic factor (BDNF). Research has indicated that the antidepressant effect of esketamine are mediated by monoamine transmitters and neurotrophic factors. Therefore, we postulate that intravenous administration of esketamine in patients with postpartum depression may alter the serum concentrations of these neurotransmitters.

**Methods** Three hundred fifteen patients with postpartum depression were selected and divided into two groups based on randomized numerical expression: esketamine (E) group (0. 25 mg/kg esketamine) and control (C) group (a same volume of 0.9% saline), all the drugs were pumped for 40 min. After the end of drug pumping, all patients were continuously observed for 2 h. Changes in serum levels of 5-HT, DA, NE, BDNF were recorded before drug administration and on the 3rd day after drug administration. The scores of Edinburgh Postnatal Depression Scale (EPDS) were calculated before drug administration, and on the 3rd day and on the 30th day after drug administration. Dizziness, headache, nausea, vomiting, drowsiness, and feeling of detachment occurred were recorded within 2 h after drug administration.

**Results** Before drug administration, the serum concentrations of 5-HT,DA,BDNF,NE in Group E and Group C were namely (0. 91 ± 0. 19 vs. 0. 98 ± 0. 21, $P = 0.181$), (2. 38 ± 0. 35 vs. 2. 32 ± 0. 32, $P = 0.491$), (3. 07 ± 0. 89 vs 3. 02 ± 0. 88, $P = 0.828$), (39. 79 ± 7. 78 vs 41. 34 ± 10. 03, $P = 0.506$). On the third day post-medication, the serum concentrations of 5-HT,DA,BDNF,NE in Group E and Group C were namely (1. 42 ± 0. 35 vs. 0. 96 ± 0. 24, $P < 0.001$), (3. 99 ± 0. 17 vs. 2. 41 ± 0. 28, $P < 0.001$),(5. 45 ± 0. 81 vs 3. 22 ± 0. 76, $P < 0.001$),(44. 36 ± 9. 98 vs 40. 69 ± 11. 75, $P = 0.198$). Before medication, the EPDS scores were (16. 15 ± 3. 02 vs 17. 85 ± 3. 89, $P = 0.064$). on the third day after medication, the Group E had significantly reduced scores (12. 98 ± 2. 39 vs 16. 73 ± 3. 52, $P < 0.001$). On the 30rd day after medication, EPDS scores between the two groups were (16. 34 ± 3. 43 vs 16. 91 ± 4. 02, $p = 0.203$). Within 2 h of medication, the rate of adverse events was similar between the two groups.

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**Conclusions** Small doses of esketamine can increase the serum concentration of 5-HT,DA,BDNF, and in the short term, decrease EPDS scores, and improve postpartum depressive symptoms.

**Trial registration** Retrospectively registered in the Chinese Clinical Trial Registry (ChiCTR2300078343, 2023/12/05).

**Keywords** Esketamine, Postpartum depression, Serum neurotransmitters

## Introduction

Postpartum depression (PPD) often develops within 6 weeks after delivery, and defined as a psychosomatic disorder with diverse clinical manifestations such as, easy to cry, feeling frustrated and irritable, among others. This condition is also aggravated by diseases and can lead to hallucinations [1]. According to statistics, the incidence of PPD in China is 15%-40. 3% [2, 3]. The etiology of PPD is multifaceted, with most researchers postulating that it is caused by a collection of psychological, physiological, social and environmental factors [4, 5]. Recent studies have demonstrated that PPD is closely related to abnormal changes in neurotransmitter levels, including the decline of serum neurotransmitters, such as 5-hydroxytryptamine (5-HT), dopamine (DA), norepinephrine (NE) [5, 6]. Brain derived neurotrophic factor (BDNF) is the most important neurotrophic factor in PPD. Research has found that BNDF contributes to the development of pain and depression and other emotional changes, leading to the occurrence of PPD [7].

As a novel antidepressant treatment drug, esketamine was approved by the U. S. Food and Drug Administration (FDA) in 2019 for the treatment of refractory depression in adults. The antidepressant effects of esketamine are also multi-mechanistic, one of which is through blocking NMDA receptors on γ-aminobutyric acid (GABA) interneurons and activating α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (α-amino-3-hydroxy-5- methyl-4-isoxazole-propionicacid (AMPA) receptor, which increases with BNDF levels, a neurotrophic signal that restores synaptic function [7, 8]. Another important pathway mediating the antidepressant effects of esketamine is the activation of monoaminergic receptors and increased release of monoamine transmitters such as 5-HT and DA [8, 9]. Over the years, esketamine is increasingly used in clinical practice for cesarean section to prevent PPD symptoms [10, 11], and other studies have reported that a lower dose of esketamine intravenously pumped for 40 min can achieve rapid and strong antidepressant effect within 24 h in patients with refractory depression [12]. A single intravenous subclinical dose of ketamine produces a strong antidepressant effect that peaks within 72 h and is maintained for approximately 1 week [13].

Therefore, we hypothesize that esketamine may have an impact on the expression levels of these neurotransmitters in the serum of PPD patients. This study will explore whether esketamine may affect the expression levels of these neurotransmitters in the serum of PPD patients.

## Methods

The manuscript was written in accordance with the CONSORT statement guideline for a randomized controlled trial.

### Study design

The study protocol was approved by the Ethics Committee of Xuzhou Central Hospital, Ethics No. XZXY-LK-20211209–050. The patients and their families were informed and asked to sign informed consent form to participate in the study. The experiment was retrospectively registered with the China Clinical Trial Centre under the registration number ChiCTR2300078343 (2023/12/05).

### Participants

Data were obtained from patients who gave birth for the first time (including natural delivery and caesarean section) in the obstetrics department of our hospital and received postnatal follow-up from December 2021 to December 2023. All patients with PPD in this study were diagnosed by a psychiatrist in the first visit when they first visited the hospital for postnatal rehabilitation examination at 6 weeks postpartum. The inclusion criteria were: patients with PPD who met the diagnostic criteria for PPD in the Diagnostic and Statistical Manual of Mental Disorders (5th edition) (DSM-V), had a EPDS score greater than or equal to 13 points; were first diagnosed with a complete history; had an education level of primary school or above; had no comorbidities or complications during pregnancy; had a Body Mass Index(BMI) range between 18-30 $kg/m^2$; voluntarily agreed to participate in the study; and signed informed consent form. The exclusion criteria were: those with previous family history of psychosis or psychiatric history; those with intellectual disability or cognitive dysfunction; patients with contraindications to esketamine such as hypertension, glaucoma; depression due to other organic diseases or post-traumatic stress; those who were allergic to esketamine; and those who could not co-operate until the end of the study.

### Randomization and blinding

We performed a randomized double-blind trial using the computerized random number table method. The parturients were randomly divided into esketamine group and control group. The group allocation and study drug regimen were hidden in sequentially numbered sealed opaque envelopes. Dispense the medication into a 20 ml syringe and labeled the syringe with the name of the parturient. On the day of the experiment, the anesthesiologist (Zhu Lijiao), who was unknown of the study protocol, opened the envelope in the order in which subject was enrolled, and check the name on the syringe one more time. Neither the anesthesiologist nor the follow-up investigator knew the grouping. This information was hidden until the follow-up completed. The follow-up of the study was conducted by Dong Yaqi. Anesthesiologists couldn't blind of the group allocation because of the possible side effects of esketamine, but the parturients and the follow-up investigator were both blind of the allocation.

### Interventions

After admission to the room, electrocardiogram (ECG), pulse oximetry (SPO2), non-invasive blood pressure (NIBP) were routinely monitored, while peripheral venous access was opened, and the patients in group E (observation group) were administered via micropumping of esketamine 0. 25 mg/kg + 0. 9% saline diluted in 20 mL for 40 min. Patients in group C (control group) received micropumping of 0. 9% saline diluted in 20 mL for 40 min. After the end of pumping, all patients were continuously observed for 2 h, and if the patients showed no adverse reactions such as dizziness, headache, nausea, vomiting, drowsiness, sense of separation, and were conscious, they were discharged from hospital accompanied by their family members.

The patients were instructed to return to the hospital on the day of drug administration (before starting the drug) and on the 3rd day after drug administration to draw 5 mL of fasting elbow vein blood in the early morning. The plasma was separated via high-speed centrifugation and stored in a -80℃ low-temperature refrigerator. Enzyme-linked immunosorbent assay (ELISA) was conducted to detect 5-HT, DA, NE, and serum BDNF levels.

All patients were transferred to the psychiatric outpatient clinic for continued evaluation and treatment at the end of this trial.

### Observational indicators

Primary outcome indicators: patients' serum 5-HT, DA, NE, and BDNF levels before and on the 3rd day after drug administration. Secondary outcome indicators: the patients' scores on the EPDS, the EPDS consists of ten items, including mood, pleasure, remorse, depression, fear, insomnia, coping ability, sadness, crying, and self injury. According to the severity of the symptoms displayed, assign 0–3 points: 0 points (never), 1 point (occasionally), 2 points (frequently), and 3 points (always), with a score range of 0–30 points. Currently, China still uses a diagnostic threshold of 13 points or greater as the diagnostic threshold. EPDS scores were recorded before, on day 3 and on day 30 after administration; the occurrence of adverse reactions, such as dizziness, headache, nausea, vomiting, drowsiness, and feeling of detachment, were recorded within 2 h after drug administration.

### Sample size and statistical analysis

The prevalence of PPD in Chinese primigravid women is approximately 27.8% [2, 3], and we hypothesized that intravenous pumping of esketamine may decrease the prevalence by 50%. In this context, setting the statistical power at 80% and = 0. 05 would yield a sample size of 262, and considering a 20% patient dropout rate. It was expected that 315 patients would be recruited in the study. This sample size is derived from the local incidence rate of postpartum depression. After the end of this study, the maximum sample size calculated based on the primary outcome measures did not exceed the initially determined sample size. Therefore, the sample size for this study is adequate.

Statistical analyses were conducted using the SPSS19. 0 software. The Shapiro–Wilk(S-W) method was employed to test whether the data obeyed a normal distribution; and normally distributed data were expressed as mean ± standard deviation ($\overline{X} \pm S$), and compared using independent samples t-tests between groups, and repeated-measures analysis of variance (ANOVA) was conducted to compare groups at different time points. Non-normally distributed data were expressed as median (M) and interquartile spacing (IQR), and the Mann–Whitney U test was utilized to compare between groups. Count data were expressed as the number of cases (percentage), and analyzed by the $\chi 2$ test or Fisher's exact probability test. The Wilcoxon rank sum test was utilized to compare hierarchical data. A test level was $\alpha = 0.05$, and the difference was considered statistically significant at $p < 0.05$.

## Results

### Patients

A total of 1, 501 patients were followed up in this study. Among them, 409 patients with PDD were screened out, including 249 patients with cesarean section, 160 patients with transvaginal delivery, 50 patients did not meet the inclusion criteria,41patients who refused to

participate in this experiment, 3 patients did not participate in this study for other reasons. A total of 315 subjects were included, 29 patients were lost to visit or withdrew from the study in the middle of the study. Finally, 282 patients were enrolled in the study, 146 patients in group E and 136 patients in group C (Fig. 1). The clinical characteristics were comparable between the two groups, and there was no significant differences in baseline data between the groups (Table 1).

**Table 1** Characteristics of our study cohort

| | Group C ($n=136$) | Group E ($n=146$) | *P*-value |
|---|---|---|---|
| Age(year) | 31. 3 ± 4. 3 | 32. 2 ± 3. 9 | 0. 0674 |
| Height(cm) | 160. 7 ± 5. 1 | 161. 8 ± 4. 8 | 0. 0637 |
| Weight(kg) | 75. 2 ± 10. 9 | 74. 6 ± 11. 2 | 0. 6489 |
| BMI (kg/m$^2$) | 25. 7 ± 3. 9 | 25. 4 ± 4. 1 | 0. 529 |
| Delivery method | | | 0. 424 |
| Cesarean section | 86(63. 2%) | 90(61. 6%) | |
| Vaginal delivery | 50(36. 8%) | 56(38.4%) | |
| Years of education received | | | 0. 843 |
| Less than 12 years | 23(16. 9%) | 26(17. 8%) | |
| More than 12 years | 113(83. 1%) | 120(82. 2%) | |
| Employment (n, %) | | | 0. 556 |
| Employed | 110(84. 6%) | 122(83. 5%) | |
| Unemployed | 26(15. 4%) | 24(16. 5%) | |
| Mode of pregnancy | | | 0. 901 |
| Natural | 129(94. 9%) | 138 (94. 5%) | |
| Unnatural | 7 (5. 1%) | 8 (5. 5%) | |
| Infant feeding | | | 0. 841 |
| Maternal | 81(59. 6%) | 89(61. 0%) | |
| Mixed | 33(24. 3%) | 37(25. 3%) | |
| Artificial | 22(16. 2) | 20(13. 7%) | |

### Primary outcome

Before drug administration, the serum concentrations of 5-HT in Group E and Group C were comparable. On the third day post-medication, there was a significant increase in serum 5-HT concentration in Group E (1. 42 ± 0. 35 vs. 0. 96 ± 0. 24, $P<0.001$) (Fig. 2A). Similar trends were observed for DA and BDNF. On the third day post-medication, the serum concentrations of DA in Group E and Group C were (3. 99 ± 0. 17 vs. 2. 41 ± 0. 28, $P<0.001$) (Fig. 2B). The serum concentrations of BDNF in Group E and Group C before medication were (3. 07 ± 0. 89 vs 3. 02 ± 0. 88, $P=0.828$), and on the third day after medication, the serum concentrations of

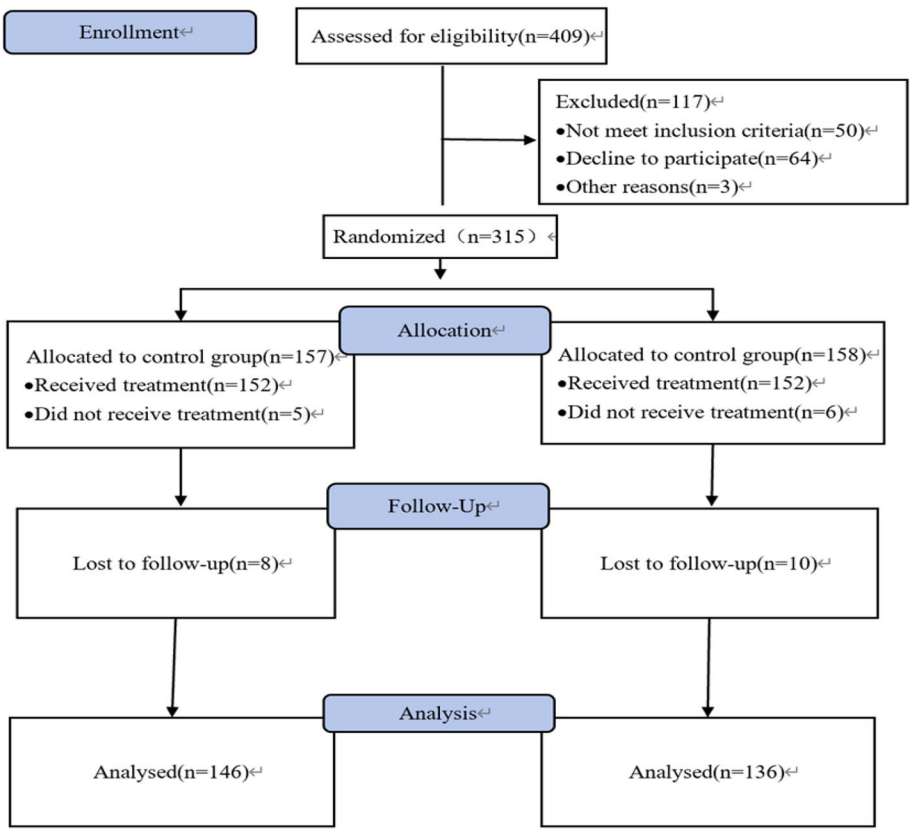


**Fig. 1** Flow diagram

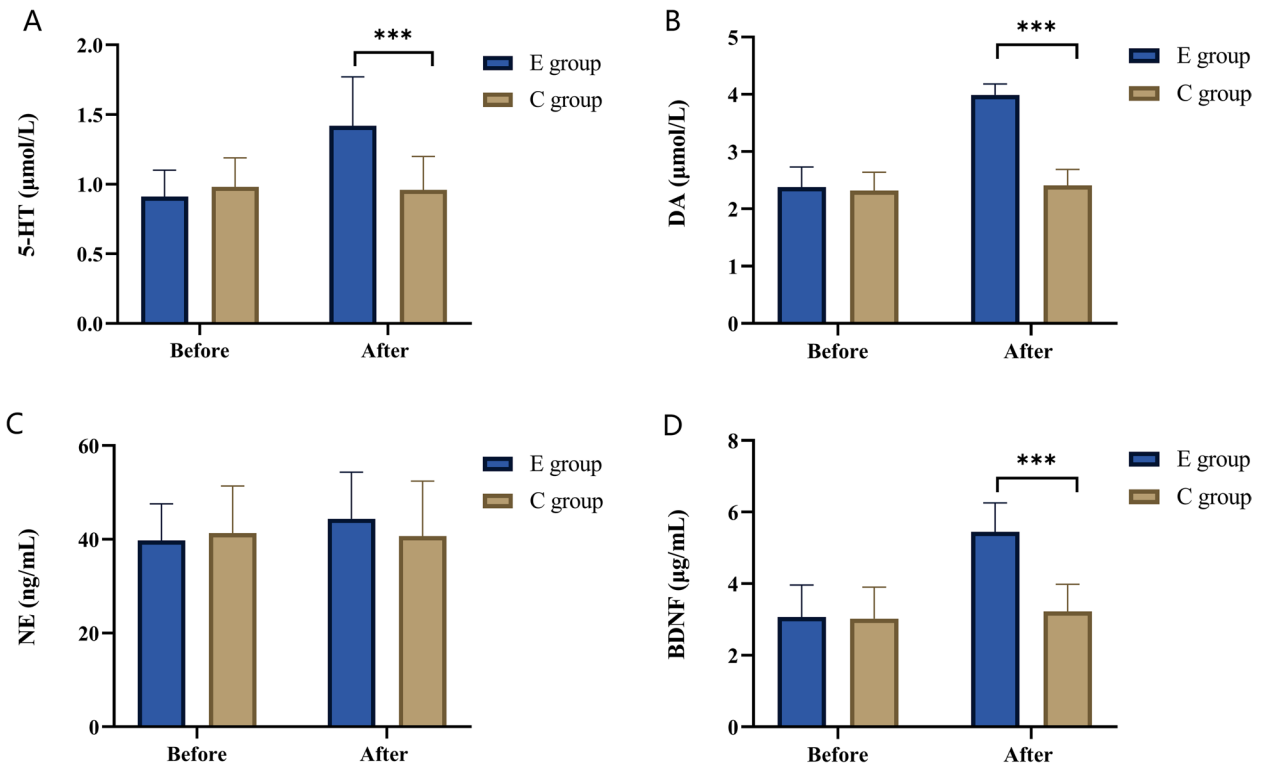


**Fig. 2** Changes in serum 5-HT/DA/NE/BDNF concentration before and after medication in the two groups. ***$P < 0.01$

BDNF in Group E and Group C were (5. 45 ± 0. 81 vs 3. 22 ± 0. 76, $P < 0.001$) (Fig. 2D). However, no differences in serum NE concentration were observed between the two groups before and after medication. (Fig. 2).

### Secondary outcome

Before medication, the EPDS scores were not significantly different between the two groups (16. 15 ± 3. 02 vs 17. 85 ± 3. 89, $P = 0.064$). However, on the third day after medication, the E group had significantly reduced scores (12. 98 ± 2. 39 vs 16. 73 ± 3. 52, $P < 0.001$). On the 30rd day after medication, there was no significant difference in EPDS scores between the two groups of patients (16. 34 ± 3. 43 vs 16. 91 ± 4. 02, $p = 0.203$) (Fig. 3). Within 2 h of medication, the rate of adverse events was similar between the two groups (Table 2).

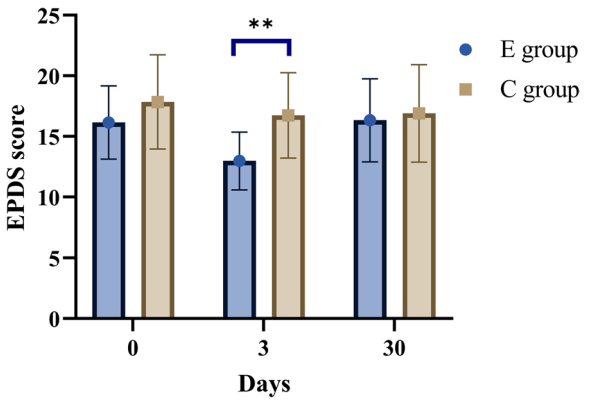


**Fig. 3** Comparison of Edinburgh Depression Scale (EPDS) scores between the two groups. **$P < 0.05$

## Discussion

In this study, a 0. 25 mg/kg dose of esketamine was found to increase the concentration of the serum neurotransmitters such as 5-HT,DA,BDNFand improve EPDS scores in the short term in patients with PPD. PPD is a psychiatric condition that manifests during the postnatal period, often referred to as the "invisible killer. " Research has shown that maternal postpartum depression can contribute to cognitive and behavioral

**Table 2** Adverse events

| Adverse events | Group C (%) | Group E (%) | Total (%) | *P*-value |
|---|---|---|---|---|
| Dizziness | 12 (8. 8) | 15 (10. 3) | 27 (9. 6) | 0. 679 |
| Headache | 8 (6. 0) | 12 (8. 2) | 20 (7. 1) | 0. 445 |
| Drowsiness | 12 (8. 8) | 16 (11. 0) | 28 (9. 9) | 0. 425 |
| Nausea | 11 (8) | 13 (8. 9) | 24 (8. 5) | 0. 806 |
| Vomit | 8 (6. 0) | 10 (6. 8) | 18 (6. 4) | 0. 740 |
| Separation sensation | 5 (3. 7) | 8 (5. 5) | 13 (4. 6) | 0. 471 |

issues in infants, posing significant challenges to families and society [14, 15]. Consequently, it is important to develop strategies for preventing and treating PPD. Researchers [16] demonstrated that PPD patients exhibited changes in hypothalamus-pituitary-adrenergic axis, neuroendocrine system dysregulation, 5-HT, DA, NE and other abnormal changes in neurotransmitters, in which 5-HT, DA, NE are decreased which induce mood abnormalities. Hare [17] and other studies have shown that activation of medial dopamine D1 receptors in the prefrontal cortex may mediate the antidepressant effects of esketamine. Cavalleri L et al. [18] found that ketamine and its enantiomer s-ketamine improved the mood of the patients by modulating the mesolimbic dopamine system (D2 and D3 receptors) and monoamine transporters. Studies [19] have demonstrated that the rapid antidepressant effects of ketamine can be reduced by the addition of a 5-hydroxytryptamine receptor antagonist, and that esketamine significantly and dose-dependently increases the release of 5-HT in the prefrontal cortex of the brain. In this study, serum 5-HT and DA were increased after 3 days of esketamine pumping, however, the concentration of NE in the observation group was not increased, which may be related to the small dosage of esketamine.

Several studies have demonstrated that esketamine's antidepressant mechanism is multifaceted. One main aspect involves blocking NMDA receptors on γ-aminobutyric acid (GABA) interneurons and activating AMPA receptors [7, 8]. This action enhances neurotrophic signaling pathways, promoting the restoration of synaptic function [20]. The AMPA receptor initiates an intracellular cascade reaction, increases the release of BDNF, and stimulates the receptor tropomyosin related kinase B (TrkB), thereby activating a series of signaling pathways and achieving antidepressant effects [21, 22]. Studies have shown [18] that BDNF in the prefrontal cortex and hippocampus will be reduced when the patient is under stress and depressed. Zhou Yingyong et al. [23]. confirmed that the serum BDNF levels of patients with PPD were reduced compared with those of healthy mothers. On the other hand, esketamine stimulates signaling pathways that enhance neuroplasticity and synaptogenesis by targeting AMPA receptors. This activation leads promotes the production of BDNF. Liu et al. found that serum BDNF levels were elevated in breast cancer patients with mild to moderate depression treated with esketamine [24]. In this study, we observed that by pumping esketamine at a dose of 0. 25 mg/kg, the value of BDNF in the patients was increased on the third day after the administration compared with levels in the control group, which is consistent with the findings by Liu et al. Therefore, we infer that the antidepressant effect of esketamine is related to its ability to stimulate the release of some neurotransmitters.

Currently, there is no standard guideline for the of intravenous dosage of esketamine in patients with depression. However, it has been shown that [25, 26] that intravenous esketamine is acceptable in the range of 0. 1–1. 0 mg/kg, while the likelihood of adverse effects increases as the dose increases. A study by Roger S et al. [27] suggested a dose of 0. 5 mg/kg with an infusion time of more than 40 min for depressed patients. Escitalopram, being an isomer of ketamine, is generally considered to be twice as potent, and therefore we postulated that if escitalopram was used, it can be pumped intravenously at a dose of 0. 25 mg/kg. In a study by Jaskaran et al. [12], it was found that in patients with refractory depression, the dose of 0. 20 mg/kg or 0. 20 mg/kg of ketamine can be administered as an intravenous infusion. For 0. 20 mg/kg or 0. 40 mg/kg of s-ketamine, a lower dose is better tolerated and a balance should be established between efficacy and the tolerability of the drug. A study by Hangyan et al. [28] found that 0. 125 mg/kg and 0. 25 mg/kg of esketamine were safe for intravenous pumping in caesarean section and both doses reduced EPDS scores and prevented PPD. In this study, the dose of 0. 25 mg/kg was adopted for 40 min vi intravenous pumping. Although few patients experienced some minor adverse effects, the overall safety was good.

Esketamine has been reported to have several adverse effects including dizziness, somnolence, nausea, vomiting, and a feeling of dissociation, while less common adverse effects include dyspepsia, dyspnoea, drug intolerance, increased blood pressure, and increased heart rate [29, 30]. Notably, these adverse effects of esketamine are mild and self-limiting. The transient increase in blood pressure and dissociative symptoms caused by esketamine peak 40 min after administration generally return to pre-dose levels within 2 h. The symptoms reported by patients in this study were mild and largely disappeared within 2 h, which also indicates that the experimental dose was safe.

A research has found that the application of esketamine during cesarean section can reduce the incidence of short-term postpartum depression (PD), with a downward trend in the incidence of long-term PD [31]. Additionally, literature reports that repeated administration of ketamine nasal spray can rapidly treat refractory depression in the short term, and its antidepressant effects persist for several weeks after discontinuation of treatment [32]. In this study, it was observed that after 3 days of medication, patients in the esketamine group showed a decrease in EPDS scores, and compared to the control group, $P<0.05$, indicating a statistically significant difference. However, one month after treatment, there was

no significant difference in EPDS scores between the two groups. Therefore, more research is needed to confirm whether single or multiple administrations of esketamine have long-term antidepressant effects.

This paper has some limitations that should be acknowledged. Firstly, we only investigated a single dose of esketamine. It is likely that other doses may affect the outcomes and safety issues. Secondly, due to conditional constraints, only a single dose was administered in the outpatient clinic, and only a single blood collection was performed after administration. Moreover, we only assessed the short-term effect of esketamine on the serum transmitters. Therefore, further experiments are needed to verify the long term effect of esketamine. Thirdly, this study is a single-center study, and a multicenter studies are needed to validate the findings.

## Conclusion

Esketamine can elevate the levels of 5-HT, DA, and BDNF in the serum of individuals with PPD, and can decrease the EPDS score swiftly, thereby ameliorating the symptoms of those with PPD. A single 0. 25 mg/kg dose intravenous pump administration of this dose was safe and effective.

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**Authors' contributions**
Wang and Zhou M have made contributions to the conception and provided the funders; Qi and Zhu have made contributions to design of the study; Jiang wrote the main manuscript text; Dong and Zheng have made contributions to interpretation of data and prepared figures; Li and Zhou H have drafted the work. All authors reviewed the manuscript.

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**Availability of data and materials**
The datasets used during the study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
The study was approved by the Ethics Committee of Xuzhou Central Hospital, Ethics No. XZXY-LK-20211209–050.Written informed consent was provided from the patients enrolled to the study.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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