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Effect of pre-administration of esketamine intraoperatively on postpartum depression after cesarean section

A randomized, double-blinded controlled trial

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Abstract

Background: To evaluate the effect of pre-administration of esketamine intraoperatively on the occurrence of postpartum depression after cesarean section under combined spinal-epidural anesthesia.

Methods: A total of 120 women aged 24 to 36 years undergoing cesarean section by spinal-epidural anesthesia with American Society of Anesthesiologists physical status II were enrolled. According to the intraoperative use of esketamine, all participants were randomly divided into 2 groups: test group (group E) and control group (group C). Esketamine was administered intravenously at a dose of 0.2 mg/kg after the infant was delivered in group E and equal volume of normal saline was given in group C. The incidence of postpartum depression was recorded at 1 week and 6 weeks after the operation. The occurrence of adverse reactions such as postpartum bleeding, nausea and vomiting, drowsiness, and nightmares were also recorded at 48 hours after surgery.

Results: Compared with group C, the incidence of postpartum depression was significantly lower at 1 week and 6 weeks after surgery in group E ($P < .01$). There was no significant difference of the adverse effects at 48 hours after the operation between the 2 groups.

Conclusion: Intravenous infusion of 0.2 mg/kg esketamine in women during cesarean section can significantly reduce the incidence of postpartum depression at 1 week and 6 weeks after surgery without increasing related adverse effects.

Abbreviations: EPDS = Edinburgh postpartum depression scale, NMDAR = N-methyl-D-aspartate receptor, PPD = postpartum depression.

Keywords: cesarean section, combined spinal-epidural anesthesia, esketamine, postpartum depression

1. Introduction

Recently, adverse events such as maternal suicide and infanticide often occur due to postpartum depression (PPD), and the mental health of women during the perinatal period has been receiving increasing attention. PPD is a common mental system disorder in obstetrics and refers to the maternal depression in the puerperium, specifically manifested as: depression, anxiety, irritability, fear, pessimism, excitement, poor coping ability and other bad emotions. PPD may occur in both primiparous and multiparous women, with its incidence about 3.5% to 33%. Six weeks after delivering is a high-risk period for postpartum depression, most of which may occur within 1 week.[1,2] The causes of PPD are complex and related to maternal genetic, physiological, psychological, family, social, and other factors. Studies have shown that maternal depressive mood, poor sleep quality, disharmonious family relations, lack of social support, trauma during pregnancy, and combined diseases are the major risk factors for PPD.[3,4] The maternal mental state of PPD is very unstable, which not only affects their own physical and mental health, but also affects the breastfeeding of infants and family harmony.

At present, the clinical treatment of PPD is mainly psychotherapy combined with drug therapy, but the research shows that long-term drug treatment may have adverse effects on the infant's cognitive, behavioral, neurological, and emotional development through lactation.[5,6] Therefore, it is even more important for the prevention of PPD. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, which is mostly used in operation of pediatric, outpatient, obstetric anesthesia, and

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Trial registration Clinical Trials Registry – Chinese (ChiCTR registration number – ChiCTR2200060387).

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perioperative assisted analgesia. In recent years, the antidepressant effect of ketamine has been paid more attention in the treatment of mental illness. Its application in patients with resistant depression has the advantage of rapidly improving depressive symptoms and significantly reducing the risk of suicide.[7,8] Esketamine is an S-enantiomer of ketamine and has about twice the affinity to N-methyl-D-aspartate receptor (NMDAR), which is a hot topic of antidepressant research.[9] Therefore, this study was designed to explore the effect of prophylactic use of esketamine during cesarean section on the incidence of maternal PPD and observe the related adverse effects to provide a reference for clinical prevention of PPD.

2. Materials and Methods

2.1. Ethics and trial registration

The consolidated standards of reporting trials recommendations were followed in this study.[10] Ethical approval for this study (2021-03-031-K01) was provided by the Institutional Ethics Committee of the Affiliated Jiangning Hospital of Nanjing Medical University. This study was registered in the Chinese Clinical Trial Registry (ID: ChiCTR2200060387) on 30th May 2022. All women involved were informed of the proposal and gave their written, informed consent.

2.2. Participants

A total of 120 primiparous women undergoing elective cesarean section from 1st April to 30th November 2022 in the Affiliated Jiangning Hospital of Nanjing Medical University were enrolled, with single term pregnancy, American society of Aneshesiologists physical status II, age 24 to 36, body mass index 24 to 30 kg/m^2. The exclusion criteria were as follows: Having mental disorder; Preoperative organic or pharmacogenic depression; Improper position of infant, breech position; Combined pregnancy complications such as hypertension and diabetes; Combined with functional insufficiency of important organs such as heart, liver, kidney and others; The anesthesia mode needed to be changed due to the failing operation of combined spinal-epidural anaesthesia; The anesthesia block plane(-temperature sense) is higher than T_4, or too low to meet the surgical requirements; ovarian cyst removal or myomectomy are added intraoperatively; Intraoperative blood loss > 500 mL; (10) operation time > 2 hour.

2.3. Study design

All of the women were divided into the test group (group E) and control group (group C) by random number tables generated through a computer, with 60 cases in each group. Esketamine (Hengrui Pharmaceutical Co., Ltd., Jiangsu, China) was administered intravenously at a dose of 0.2 mg/kg in 10 minutes after the infant was delivered in group E and equal volume of normal saline was given in group C. Neither observers nor subjects were aware of the grouping condition, and the drug was dissolved in 100 mL of normal saline by an anesthesia nurse who was not aware of the grouping condition as well.

2.4. Sample size

Based on the results of our preexperiment (10 participants in each group), the incidence of PPD at 6 weeks after the operation can be reduced by 10% in the test group. Power analysis showed that a reduction rate of 10% with $\alpha = 0.05$ and a 10% dropout rate within a power value of 90%, a sample size of at least 52 per group was needed. Sixty samples for each group were designed in this study. Figure 1 showed the consolidated standards of reporting trials flow diagram of the study participants' recruitment.

2.5. Randomization and allocation concealment

This study was conducted in the Jiangning Hospital Affiliated to Nanjing Medical University in the period from 1st April 2022 to 30th November 2022. Patients were randomly assigned in 2 groups. Random tables were generated using SPSS version 20.0 (IBM SPSS Inc., Chicago, IL). One hundred and twenty sealed envelopes were prepared by a statistician who did not participate in the study. The study was performed with neither patients nor the observers awareness of the group to which each patient belonged. To assure concealment of allocation, numbers were kept in sealed and opaque envelopes, which were opened by an anesthesiologist who was not involved in this study.

2.6. Interventions and outcome measures

All women fasted for 12 hours and fasted in liquid 4 hours before the operation without any medication. After entering the operating room, peripheral venous access was opened, maternal electrocardiography, heart rate, noninvasive blood pressure measurement, and pulse oximetry were monitored, and oxygen for 5 L/minutes by the mask were received. Combined spinal-epidural anesthesia were operated in all women between L_3 and L_4. A dose of 0.5% bupivacaine 8 to 10 mg were used in the subarachnoid space within 20 seconds, and an epidural lumen tube was imbedded for 4 cm. Temperature perception block plane was determined 10 minutes later, too high (above T_4) or too low (unable to meet the surgical requirements, requiring local anesthetic supplementation by epidural catheter) were excluded from this study. All anesthesia-related operations were completed by the same anesthesiologist, and the surgery was performed by the same group of obstetricians. Esketamine was used intravenously at a dose of 0.2 mg/kg (dissolved in 100 mL of normal saline) in 10 minutes after the infant was delivered in group E and equal volume of normal saline was given in group C. Patient controlled intravenous analgesia pump was used in both groups. The formula was as follows: 1.0 g/kg sufentanil combined with 4 mg tropisetron to 100 mL with normal saline, loading dose: 5 mL, background infusion rate: 2 mL/hours, bolus: 1 mL, lockout time: 15 minutes.

The occurrence of PPD at 1 week and 6 weeks after surgery were evaluated and recorded. The diagnostic criteria for PPD are usually defined in 2 steps: firstly, Edinburgh postpartum depression scale (EPDS) was used to screen for suspicious patients (score > 9);[11] secondly, suspicious patients were strictly tested according to the clinical protocol interview. The standard for the diagnosis of PPD was consulted by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).[12] The screening and diagnosis were determined by different physicians who did not know the grouping. The occurrence of adverse reactions such as postpartum bleeding, nausea, vomiting, drowsiness, and nightmares in 48 hours after the operation was recorded by anesthesia nurses who were not aware of the grouping as well.

2.7. Statistics

Data analysis was performed by the SPSS 20.0 statistical software package, version 20.0 (SPSS Inc., Chicago, IL). Continuous variables were presented as mean ± SD, and differences between the 2 groups were analyzed with mutual comparison by single factor variance analysis (1-way ANOVA). The incidence of PPD and adverse reactions were considered as categorical variables, which were analyzed with a χ^2 test. It was considered statistically significant since a P value < .05.

3. Results

In this study, 120 cases were initially screened, and 5 cases were excluded. In group C, 1 case was excluded for intraoperative bleeding > 500 mL, 1 case was excluded for surgery of ovarian cyst, and another participant was excluded due to fail of anesthetic puncture; in group E, 1 case was excluded for intraoperative bleeding > 500 mL, and another participant was excluded due to fail of anesthetic puncture. In total, 57 cases in group C and 58 cases in group E were included in the statistical analysis (Fig. 1).

Women in 2 groups shared similar demographic characteristics (age, gestational week, body mass index, time of operation, intraoperative bleeding and infusion) (Table 1).

Compared with group C, the incidence of PPD in group E was significantly lower (1 week: 15.8% vs 3.4%; 6 weeks: 19.3% vs 5.2%) ($P < .01$). There were no significant differences between the 2 groups on adverse effects, including postpartum hemorrhage, nausea, vomiting, drowsiness, and nightmares during 48 hours after the operation (Table 2).

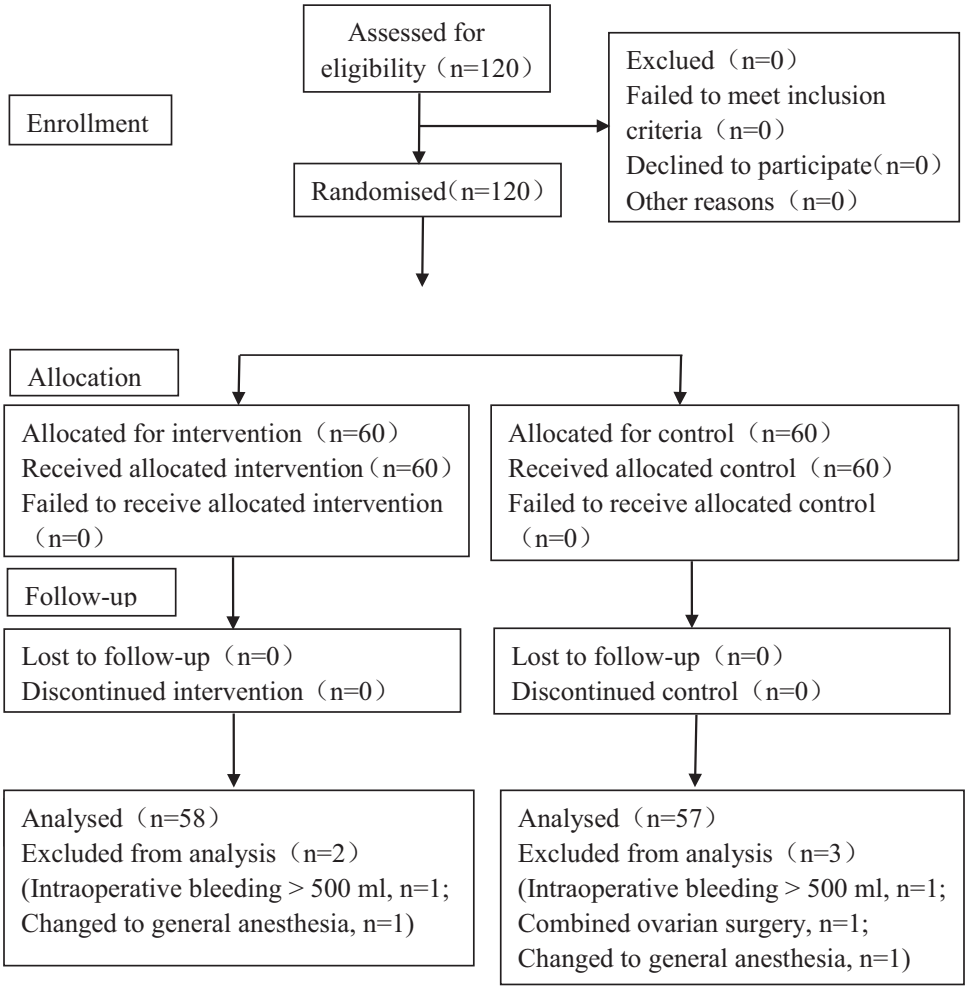

Figure 1. In this study, 120 cases were initially enrolled, and 5 cases were excluded. In total, data of 57 cases in group C and 58 cases in group E were analyzed. CONSORT, the Consolidated Standards of Reporting Trials. CONSORT = the consolidated standards of reporting trials.

Table 1

Characteristics of women in the 2 groups.

Characteristics	Group C (n = 57)	Group E (n = 58)	*P* value
Age (yr)	27.9 ± 4.1	28.3 ± 4.9	.769
Gestational age (wk)	39.1 ± 2.3	38.7 ± 3.6	.125
Height (cm)	157.6 ± 6.5	159.1 ± 7.1	.228
Weight (kg)	66.5 ± 5.8	65.8 ± 5.2	.836
BMI (kg/m^2)	27.6 ± 3.7	26.9 ± 4.4	.556
Duration of operation (min)	42.8 ± 4.7	40.9 ± 5.9	.189
Intraoperative bleeding loss (mL)	316 ± 33	302 ± 39	.437
Intraoperative transfusion volume (mL)	1285 ± 47	1317 ± 35	.335

Data are presented as mean ± SD. continuous variables were compared by mutual comparison after single factor variance analysis (one-way ANOVA).
BMI = body mass index.

Table 2

Occurrence of PPD and adverse reactions in the 2 groups.

Group	PPD		Postpartum hemorrhage	Nausea, vomiting	Drowsiness	Nightmares
	1 week	6 weeks				
Group C (n = 57)	9 (15.8)	11 (19.3)	1 (1.8)	4 (7.0)	1 (1.8)	3 (5.3)
Group E (n = 58)	2 (3.4)*	3 (5.2)*	2 (3.4)	3 (5.2)	1 (1.7)	2 (3.4)
P value	.002	.004	.656	.463	.866	.532

Data are presented as n (%), mutual comparison by χ^2 test.

PPD = postpartum depression.

* Compared with Group C, $P < .01$.

4. Discussion

The DSM-IV recommended by the American Psychiatric Association and the World Health Organization (WHO) defined perinatal depression as: no previous history of mental illness, during pregnancy or childbirth within 1 to 2 weeks, 4 to 6 weeks of depressive episode symptoms, such as emotional instability, severe anxiety, panic, crying and others.[12] Women undergoing cesarean section had specific psychological activities during delivery, which might be affected by surgical stress, fetal suction and other factors. Psychological degeneration and emotional vulnerability after delivery led to a higher incidence of PPD in non-vaginal delivery than women with vaginal delivery.[13] Therefore, the incidence of PPD at 1 week and 6 weeks after cesarean section was observed in this study.

4.1. Diagnosis and treatment of PPD

Maternal depression mood was not the same as PPD. The former was mainly screened through the depression score scale, and was commonly used as EPDS, while the latter was a mental disorder that needed to be diagnosed by clinical routine examination and interview.[14] In this study, further diagnosis was made by psychiatric professionals after preliminary screening of PPD diagnostic criteria according to the EPDS score. Women with PPD had less breastfeeding, less interaction with infants, leading to an increased risk of illness, slow intellectual development of infants, and even maternal suicide or infanticide.[15] Over the years, relevant experts around the world have conducted a lot of studies on the pathogenesis of PPD, and still failed to fully define the specific pathogenesis of PPD, which might be related to genetic, neuroendocrine, immune and psychosocial factors.[16,17] PPD was mainly treated by antidepressants, such as SSRIIS (selective 5-HT reuptake inhibitors), NaSSA (NE and specific 5-HT reuptake inhibitors), SNRI (5-HT and NE reuptake inhibitors), NDRI (NE/DA reuptake inhibitors), but there were some problems of traditional drug treatment, such as slow onset, low remission rate, influence of lactation, and many adverse reactions.[18,19]

4.2. Antidepressant effect of esketamine

In recent years, ketamine had been found for its fast onset, long action time, and effect on refractory depression.[7,8] Unlike the mechanism of 5-HT reuptake inhibitors, ketamine was an NMDA receptor antagonist, which provided a new target for the development of novel antidepressants. Berman et al[20] found that depressive symptoms were significantly improved within 72 hours after receiving a subanesthetic dose (0.5 mg/kg) of ketamine. Esketamine was an S-enantiomer of ketamine, with approximately twice higher affinity to the NMDA receptor.[9] Therefore, 0.2 mg/kg of esketamine was designed in this study. In the study of Bahji et al,[21] esketamine rapidly improved depressive symptoms from 2 to 4 hours after intravenous injection. Esketamine had been approved for the treatment of depression by FDA in the US. The study of Swainson et al[22] showed that intravenous injection of esketamine was similar with ketamine for antidepressant effects, but the former might be superior of the long-term safety data. The results of this study showed that the incidence of PPD was significantly lower in group E, which confirmed the antidepressant effect of esketamine. The antidepressant effect of esketamine could last from 3 to 7 days, which might be related to the antidepressant effect of its metabolite (normethylketamine).[23]

The antidepressant mechanism of esketamine is unclear now, which has been recognized as follows: The radioligand-binding properties of NMDAR are specifically altered in depressed patients. Esketamine can block NMDAR isoforms and the elongation factor 2 kinase in eukaryotic cells, dephosphorylate elongation factor 2, increase the expression of tropommyosin receptor kinase B, and ultimately increase the release of neurotrophic factor (BDNF) to improve neural plasticity and synapse formation.[24] Esketamine can also reduce the inhibition of the presynaptic glutamatergic pathway by inhibiting the activity of γ-aminobutyric acid (GABA), leading to an increased release of presynaptic membrane glutamate, resulting in an excitation of a-amino-3-hydroxy-5-methyl-4 isooxazole propionic acid receptor (AMPAR), following a series of intracellular biochemical reactions to produce antidepressant effects.[25] In addition, a recent animal experiment showed that esketamine could inhibit autophagy through mTOR-BDNF signaling, thus reducing neuroinflammation induced by lipopolysaccharide, mainly decreasing inflammation-related cytokines (TNF-, IL-1, IL-6), apoptotic factors and autophagic marker levels, to deliver antidepressant effects.[26]

As an anesthetic drug, esketamine has been used for many years, but there were no sufficient data for the prevention or treatment of psychiatric disorders. Considering the possible risk of hallucinogenic effects and abuse of esketamine, the dose used in this study was slightly lower than the subanesthetic dose, and esketamine was only injected intravenously once. Results of follow-up showed that there were no significant differences of the occurrence of adverse reactions at 48 hours after surgery between the 2 groups.

4.3. Limitations

There are some limitations in the study. Due to possible effects of narcotic drugs, PPD after cesarean section under general anesthesia were not observed in this study. Furthermore, the severity of PPD was not observed in the study, which will be the content of future studies.

5. Conclusion

The prophylactic use of 0.2 mg/kg esketamine can significantly reduce the incidence of PPD at 1 and 6 weeks after cesarean

section without increasing related adverse effects, which can provide a reference for clinical prevention of PPD.

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