Clinical Trial/Experimental Study

Medicine

OPEN

Effects of esketamine on analgesia and postpartum depression after cesarean section

A randomized, double-blinded controlled trial

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Abstract

Background: The aim of this randomized double-blind placebo controlled clinical trial was to investigate the effects of different doses of esketamine combined with sufentanil for postoperative intravenous controlled analgesia after cesarean section and the incidence of postpartum depression.

Methods: One hundred and sixty patients undergoing elective cesarean section, with a singleton term pregnancy and American Society of Anesthesiologists physical status II were selected. All patients were treated by a combined epidural with spinal anesthesia. They were randomly divided into 4 groups according to patient controlled intravenous analgesia formula. The consumption of sufentanil, times of effective press and remediate analgesia at 48 hours after cesarean section, incidence of postpartum depression (PPD) at 1 week and 6 weeks after the operation were recorded.

Results: Comparison of cumulated dosage of sufentanil, times of effective press and rescue analgesia at 48 hours after operation: Group H was significantly lower than Group M, Group L, and Group C ($P < .05$), Group M significantly lower than group L and Group C ($P < .05$), and Group L significantly lower than Group C ($P < .05$). Comparison of the incidence of PPD at 1 week and 6 weeks later: Group H was significantly lower than Group M, Group L, and Group C ($P < .01$), Group M significantly lower than Group L and Group C ($P < .01$) and Group L significantly lower than Group C ($P < .01$). Compared with Group C, the incidence of nausea and vomiting was significantly reduced in Group H, Group M, and Group L ($P < .05$).

Conclusion: Esketamine combined with sufentanil used for patient controlled intravenous analgesia after elective cesarean section can reduce the consumption of sufentanil, improve postoperative analgesia, decrease the incidence of PPD at 1 week and 6 weeks and postoperative nausea and vomiting.

Abbreviations: EPDS = the Edinburgh Postpartum Depression Scale, NMDAR = N-methyl-D-aspartate receptor, PCIA = patient controlled intravenous analgesia, PPD = postpartum depression.

Keywords: cesarean section, esketamine, postoperative analgesia, postpartum depression

1. Introduction

In recent years, 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 receives increasing attention. PPD is a common mental system disease in obstetrics and refers to the maternal depression in the puerperium period, 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 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 research shows that long-term drug treatment may have adverse effects on the infant's cognitive, behavioral, neurological, and emotional development through lactation.[3,4] Therefore, it is even more important for the prevention of PPD.

As an S-enantiisomer of ketamine and about twice the affinity to N-methyl-D-aspartate receptor (NMDAR), esketamine is mostly used in operations of pediatric, outpatient, obstetric

This study was conducted in the Affiliated Jiangning Hospital of Nanjing Medical University with departmental funding only.

The authors have no conflicts of interest to disclose.

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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How to cite this article: Wang W, Xu H, Ling B, Chen Q, Lv J, Yu W. Effects of esketamine on analgesia and postpartum depression after cesarean section: A randomized, double-blinded controlled trial. Medicine 2022;101:47(e32010).

Received: 22 June 2022 / Received in final form: 3 November 2022 / Accepted: 3 November 2022

http://dx.doi.org/10.1097/MD.0000000000032010

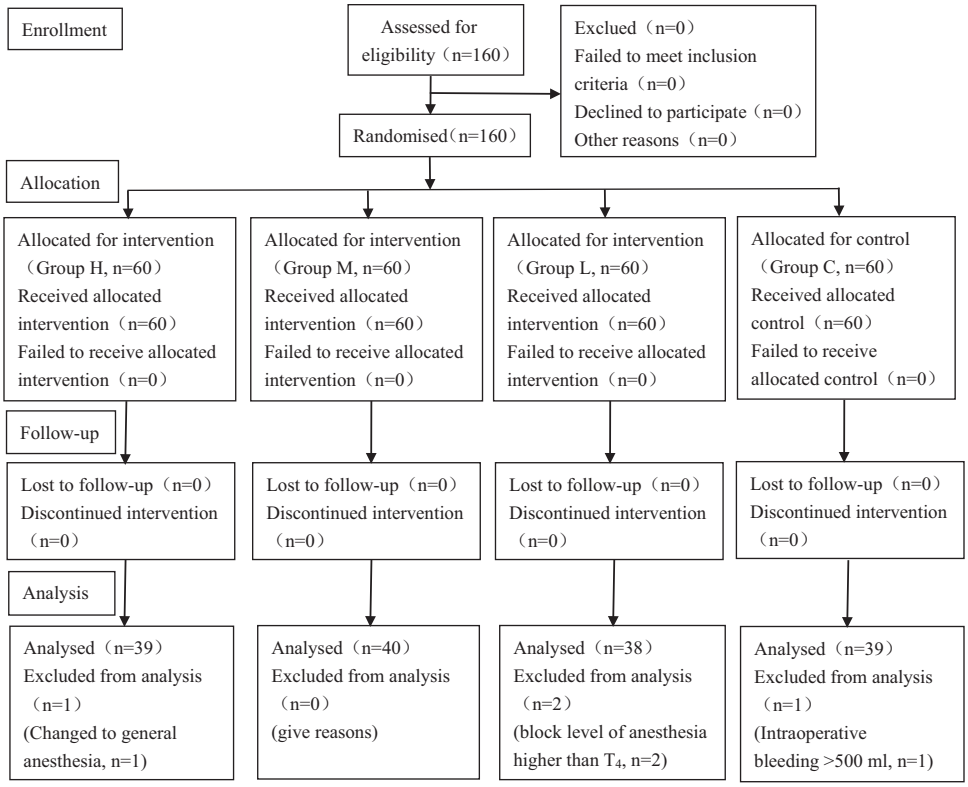

Figure 1. CONSORT flow diagram. In total, 160 patients were enrolled for this study. Four cases were excluded from the trial (one patient was excluded due to intraoperative bleeding greater than 500 mL in Group C; two patients were excluded in group L due to the block level of anesthesia higher than T_4; one patient in Group H was excluded for the change to general anesthesia.), and 156 patients' data were analyzed. CONSORT = the Consolidated Standards of Reporting Trials.

anesthesia, and perioperative assisted analgesia, which is also a hot topic of antidepressant research.[5] However, there are no reports of esketamine application with postpartum depression. The aim of the present study was to explore the effects of different doses of esketamine on postoperative analgesia and postpartum depression after cesarean section.

2. Materials and methods

2.1. Ethics and trial registration

The recommendations of the Consolidated Standards of Reporting Trials were followed in this study.[6] Ethical approval for this study (2021-03-031-K01) was provided by the Institutional Ethics Committee of the Jiangning Hospital Affiliated to Nanjing Medical University, and this study was registered in the Chinese Clinical Trial Registry (ID: ChiCTR2200060387) on April 7, 2021. All patients involved provided informed consent prior to the study.

2.2. Participants

One hundred and sixty full-term maternity patients with American Society of Anesthesiologists physical status II, aged 22 to 35 years old, and undergoing general anesthesia for elective surgical procedures were enrolled. The exclusion criteria were as follows: having a 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 anesthesia, the block level of anesthesia (thalposis) was higher than T_4, or too low to meet the operation, the duration of operation was more than 2 hours, and the intraoperative bleeding was more than 500 mL.

2.3. Sample size

Based on the results of our pre-experiment (10 participants in each group), the incidence of PPD at 6 weeks after the operation can be reduced by 10% in the esketamine 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 shows the Consolidated Standards of Reporting Trials flow diagram of the study participants' recruitment.

2.4. Randomization and allocation concealment

This study was conducted in the Jiangning Hospital Affiliated to Nanjing Medical University in the period from May 2, 2021 to December 31, 2021. Patients were randomly assigned to one of 4 groups. Random tables were generated using SPSS 20.0. One hundred and sixty 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.

2.5. Interventions and outcome measures

Patient controlled intravenous analgesia (PCIA) was used for all women after surgery, who were not informed of the specific

formulation of the analgesic pump. The configurations of PCIA in the 4 groups were as follows: control (Group C: sufentanil 1.5 μg/kg + totanisoltron 4 mg, diluted to 150 mL with saline); low dose (Group L), middle dose (Group M) and high dose (Group H) added 0.1, 0.2, and 0.4 mg/kg respectively based on Group C. All pumps were set with a bolus of 5 mL, continuous infusion amount of 2 mL/h, single dose of 1 mL, locking time of 15 minutes, and analgesia duration of 48 hours. The pump was configured by an anesthesiologist who was unaware of the enrollment.

All women fasted for 12 hours and liquid fasted 4 hours before operation without any medication. After entering the operating room, peripheral venous access was opened, maternal electrocardiography (ECG), heart rate (HR), noninvasive blood pressure measurement (NBP), and pulse oximetry (SpO_2) were monitored, and oxygen for 5 L/min by the mask were received. Combined spinal-epidural anesthesia were performed for all women between L_3 and L_4. A dose of 0.5% bupivacaine 8 to 10 mg was 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) which 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. The analgesic pump was connected at the time of surgical suture. When the static Visual Analogue Scale ≥ 4 or dynamic (cough) Visual Analogue Scale score ≥ 6, and patients' controlled press still could not relieve the pain within 48 hours after surgery, tramadol was administrated intravenously at a dose of 50 mg. The primary outcomes such as times of effective press, total sufentanil consumption and rescue analgesia within 48 hours after surgery were recorded. According to the Edinburgh Postpartum Depression Scale (EPDS), PPD at 1 week and 6 weeks after surgery were assessed. The secondary outcomes such as occurrence of nausea, vomiting, skin itching, nightmares, and diplopia were also recorded within 48 hours after surgery.

2.6. Statistics

Data analysis was performed using the SPSS 20.0 statistical software package, version 20.0 (SPSS Inc., Chicago, IL). Continuous variables were presented as mean ± SD, the gestational age was expressed in median with interquartile range (IQR), and differences between groups were analyzed with mutual comparison by one-way ANOVA. Fisher's least significant difference (LSD) test was used to do pairwise comparison between groups. The incidence of PPD and adverse reactions were considered as categorical variables, which were presented as n (%) and analyzed with a χ^2 test. It was considered statistically significant since a $P < .05$.

3. Results

In total, 160 patients were enrolled for this study. 4 cases were excluded from the trial (one patient was excluded due to intraoperative bleeding greater than 500 mL in Group C; two patients were excluded in Group L due to the block level of anesthesia higher than T_4; one patient in Group H was excluded for the change to general anesthesia.), and 156 patients' data were analyzed (Fig. 1).

For this study, demographic characteristics (e.g., age, gestational age, height, body weight, body mass index, and duration of operation) were similar among the 4 groups (Table 1).

Compared with Group C, times of effective press, consumption of sufentanil and rescue analgesia rate were significantly reduced in Group L, M, and H ($P < .05$). Compared with Group L, times of effective press and consumption of sufentanil were significantly reduced between Group M and Group H ($P < .05$). Compared with Group M, times of effective press and consumption of sufentanil were significantly reduced within 48 hours after surgery in Group H ($P < .05$). There was no significant difference of rescue analgesia rates within 48 hours among Group L, M, and H (Table 2).

Table 1

Characteristics of patients in the 4 groups.

Characteristics	Group H (n = 39)	Group M (n = 40)	Group L (n = 38)	Group C (n = 39)	*P* value
Age (yr)	27.9 ± 6.1	28.3 ± 5.9	28.8 ± 6.4	29.1 ± 5.5	.518
Gestational age (wk)	39.1 (38.1–40.6)	39.3 (38.4–41.2)	39.5 (38.5–40.9)	39.4 (38.3–41.2)	.733
Height (cm)	157.6 ± 6.5	159.1 ± 7.1	156.7 ± 8.2	156.8 ± 7.8	.349
Weight (kg)	66.5 ± 7.8	65.8 ± 8.2	68.3 ± 7.2	67.3 ± 6.9	.556
BMI (kg/m^2)	27.6 ± 5.7	26.9 ± 5.2	26.9 ± 5.4	27.1 ± 6.1	.627
Duration of operation (min)	42.8 ± 7.7	40.9 ± 6.9	44.1 ± 7.9	45.2 ± 8.1	.812

Values are presented as mean ± SD and median with interquartile range (gestational age), mutual comparison by single factor variance analysis (one-way ANOVA), BMI = body mass index.

Compared with Group C, the incidence of PPD at 1 week and 6 weeks and postoperative nausea and vomiting was significantly lower in Group L, M, and H ($P < .01$). Compared with Group L, the incidence of PPD at 1 week and 6 weeks was significantly deceased in Group M and Group H ($P < .01$). There was no significant difference in the incidence of PPD at 1 week and 6 weeks after surgery between Group M and group H. The incidence of nausea and vomiting within the 48 hours after the operation was similar among Group L, M, and H. There was no significant difference in the occurrence of itch skin, nightmares, and diplopia in the 4 groups (Table 3).

4. Discussion

The present data show that using esketamine combined with sufentanil for PCIA after cesarean section can effectively reduce consumption of sufentanil and incidence of PPD at 1 week and 6 weeks after surgery.

4.1. Analgesic effect of esketamine

Esketamine is an s-enantioisomer of ketamine, with a greater affinity to the NMDAR, and its analgesic efficacy is approximately 1.5 to 2 times of ketamine.[7] Compared with opioids, esketamine has no significant effect of respiratory inhibitory, so it is used in pediatric anesthesia, obstetric anesthesia and auxiliary analgesia.[8] The results of this study showed that postoperative analgesia combined with esketamine can significantly reduce the amount of sufentanil and effective presses, and high-dose esketamine was significantly superior to medium and low doses. In addition, the rate of postoperative rescue analgesia and the occurrence of nausea and vomiting in the test group were significantly lower than those in the control group. It may be related to the combination of esketamine, which had reduced the overall amount of sufentanil. There was no difference among the rate of postoperative rescue analgesia in the patients with esketamine group, which may be related to the more perfect analgesia regimen, and patients can be relieved by controlled press.

The possible mechanisms by which esketamine can assist opioids with analgesic effect were as follows: continuous infusion of subanesthetic doses of esketamine can further reduce the hyperactivation of the ascending nociception conduction pathway and reduce the release of pain-causing substances such

Table 2

Postoperative analgesia and consumption of sufentanil in the 4 groups.

Group	Effective press (times)*	Consumption of sufentanil (μg)*	Rescue analgesia [n (%)]†
Group H (n = 39)	1.6 ± 0.6‡§‖	60.6 ± 1.2‡§‖	1 (2.6)‡
Group M (n = 40)	2.9 ± 0.7‡§	63.4 ± 3.8‡§	2 (5.0)‡
Group L (n = 38)	4.1 ± 0.8‡	66.8 ± 5.1‡	2 (5.3)‡
Group C (n = 39)	5.4 ± 1.0	72.0 ± 4.4	9 (23.1)
P value	.002	.006	.004

*Values are presented as mean ± SD, mutual comparison by single factor variance analysis (one-way ANOVA). Fisher's least significant difference (LSD) test was used to do pairwise comparison between groups.

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

‡Compared with Group C, $P < .05$.

§Compared with Group L, $P < .05$.

‖Compared with Group M, $P < .05$.

as dyrophins in the spinal cord,[9] it may be related to the role of the NMDAR in morphine tolerance,[10] it has been reported that the effect of small-dose esketamine on NMDAR should not be considered as "analgesia," but be considered as "anti-pain allergy," "anti-abnormal pain" and "protective effect against tolerance."[11]

4.2. Antidepressant effect of esketamine

PPD is a common mental illness in the puerperium period. This depression includes anxiety, depression, pessimism and other bad emotions, causing serious adverse effects on the maternal body, which mostly occurs in 1 week and 6 weeks postpartum.[12] Women undergoing cesarean section have specific psychological activities during childbirth, which may be affected by surgical stress, fetal suction and other factors. Psychological degeneration and emotional vulnerability after delivery cause a higher incidence of maternal PPD in non-vaginal delivery than women with vaginal delivery.[13] Studies have shown that esketamine can improve depressive symptoms rapidly at 2 and 4 hours, with a significant dose-response relationship, although the frequency or dose was decreased, even during the follow-up phase of unadministration.[14,15] It was similar in the present study that incidence of PPD in the high dose group was significantly lower than the low dose group and had a longer duration, which may be related to the continuous background dose infusion of PCIA. The elimination half-life of esketamine was only 1 hour to 3 hours, but studies showed that its antidepressant effect can last for 3 to 7 days. It was speculated that its main metabolite demethylketamine also had antidepressant effects.[16]

It has been shown that the radioligand-binding properties of NMDAR are specifically altered in depressed patients, suggesting that NMDAR antagonists may have antidepressant effects.[17] Esketamine has greater affinity to NMDAR, and its antidepressant mechanisms are mainly as follows: It blocks the NMDAR isoform and the elongation factor 2 (eEF2) kinase sustainably in eukaryotic cells, dephosphorylates eEF2, increases the expression of tropomyosin receptor kinase B (TrkB), and ultimately increases the release of neurotrophic factor (BDNF) to improve neural plasticity and synapse formation,[18] Esketamine can induce the activation of the target of rapamycin protein complex 1(Mtorc1) signaling pathway and the extracellular regulatory protein kinase(ERK),[19] and It is also possible to improve mood by regulating the midbrain dopamine system (D2 receptors and D3 receptors), opioid receptors, and monoamine transporters.[20]

4.3. Limitations

There are some limitations in this study, such as it is subjective for using the EPDS to evaluate PPD, but there is no better evaluation method. To reduce the subjective differences, the EPDS was judged by the same anesthesiologist, who did not know the enrollment in this study. Furthermore, the severity of PPD was not compared in this study, which will be the content of further studies.

5. Conclusions

Esketamine combined with sufentanil used for patient controlled intravenous analgesia after elective cesarean section can reduce the consumption of sufentanil, improve the analgesic effect, and reduce the incidence of PPD at 1 week and 6 weeks after surgery, without increasing the related adverse effects.

Acknowledgments

This work was supported by the Department of Anesthesiology, the Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing, Jiangsu, China.

The authors affirm that they have listed everyone who contributed significantly to the work in the Acknowledgements.

Author contributions

WW, HX, and WY designed the study; JL supervised the practical carrying out of the clinical trial; WW and QC analyzed the data; WW and BL wrote the manuscript; All authors read and approved the final manuscript.

Table 3

The occurrence of PPD and side-effects in the 4 groups.

Group	Occurrence of PPD		Nausea and vomiting	Skin itching	Nightmares	Diplopia
	1 week	6 weeks				
Group H (n = 39)	0 (0)*†	1 (2.6)*†	3 (7.7)*	0 (0)	0 (0)	0 (0)
Group M (n = 40)	0 (0)*†	2 (5.0)*†	4 (10.0)*	0 (0)	0 (0)	0 (0)
Group L (n = 38)	5 (13.2)*	7 (18.4)*	4 (10.5)*	0 (0)	0 (0)	0 (0)
Group C (n = 39)	12 (30.1)	14 (35.9)	11 (28.2)	1 (2.6)	0 (0)	0 (0)
P value	.003	.001	.008	.549	1.00	1.00

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

PPD = postpartum depression.

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

†Compared with Group L, $P < .01$.

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