Effects of esketamine on analgesia and postpartum depression after cesarean section
A randomized, double-blinded controlled trial

Wei Wang, MDa, Huaxua, Bachelor’s Degreeb, Bin Ling, Bachelor’s Degreea, Qing Chen, Bachelor’s Degreea, Jie Lv, Master’s Degreea,* Wanyou Yu, Bachelor’s Degreea

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. 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. Therefore, it is even more important for the prevention of PPD.

As an S-enantiomer of ketamine and about twice the affinity to N-methyl-D-aspartate receptor (NMDAR), esketamine is mostly used in operations of pediatric, outpatient, obstetric...
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 T4; 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. 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. 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 pharmacogenetic 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 T₄, 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

---

### CONSORT Diagram Details

- **Enrollment**: 160 patients were enrolled for the study.
- **Assessment for eligibility (n=160)**: Included all patients.
- **Randomized (n=160)**: Paired the participants.
- **Analysis**: 156 patients were included in the analysis.

### Groups Description

- **Group H (n=60)**: Allocated for intervention,
- **Group L (n=60)**: Allocated for control.
- **Group C (n=60)**: Allocated for intervention.
- **Group M (n=60)**: Allocated for control.

- **Exclusions**:
  - Failed to meet inclusion criteria (n=0)
  - Declined to participate (n=0)
  - Other reasons (n=0)

### Reasons for Exclusion

- **Lost to follow-up**:
  - Failed to receive allocated intervention (n=0)
  - Discontinued intervention (n=0)
  - Excluded from analysis (n=0)

- **Analysis**:
  - Analysed (n=139)
  - Excluded from analysis (n=1)
  - Changed to general anesthesia, n=1)

### Notes

- **ChiCTR2200060387** on April 7, 2021.
- Approval for this study (2021-03-031-K01) was provided by the Institutional Ethics Committee of the Jiangning Hospital Affiliated to Nanjing Medical University.
- One hundred and sixty密封 envelopes were prepared by a statistician who did not participate in the study.
formulation of the analgesic pump. The configurations of PCIA in the 4 groups were as follows: control (Group C: sufentanil 1.5 μg/kg + tolanisoltron 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 (SpO₂) were monitored, and oxygen for 5 L/min by the mask were received. Combined spinal-epidural anesthesia were performed for all women between L₁ and L₄. 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 T₄) 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 χ² 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 T₄; 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).

| 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     | 39.1            | 39.3            | 39.5            | 39.4            | .733    |
| (wk)                | (38.1–40.6)     | (38.4–41.2)     | (38.5–40.9)     | (38.3–41.2)     |         |
| 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/m²)         | 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 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).

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
1 hour to 3 hours, but studies showed that its antidepressant action of PCIA. The elimination half-life of esketamine was only which may be related to the continuous background dose infusion of NMDAR should not be considered as “analgesia,” but be considered as “anti-pain allergy,” “anti-abnormal pain” and “protective effect against tolerance.”

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.

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 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 one-way ANOVA. Fisher’s least significant difference (LSD) test was used to do pairwise comparison between groups.
§Compared with Group L, P < .05.
#Compared with Group C, P < .05.
†Compared with Group M, P < .05.

Table 3

| The occurrence of PPD and side-effects in the 4 groups. |
|-------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Group                  | 1 week          | 6 weeks         | Nausea and vomiting | Skin itching | Nightmares | Diplopia |
| 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             | 5.49         | 1.00       | 1.00       |

*Values are presented as n (%), mutual comparison by χ² test.
PDD = postpartum depression.
†Compared with Group C, P < .01.
‡Compared with Group L, P < .01.
Data curation: Wei Wang, Bin Ling, Qing Chen.
Formal analysis: Qing Chen.
Investigation: Wei Wang, Hua Xu, Bin Ling, Wanyou Yu.
Methodology: Wei Wang, Hua Xu.
Project administration: Wei Wang, Jie Lv, Wanyou Yu.
Software: Bin Ling, Qing Chen.
Supervision: Jie Lv.
Writing – original draft: Wei Wang.
Writing – review & editing: Jie Lv.

References

[1] Wan Mohamed Radzi CWJB, Salarzadeh Jenatabadi H, Samsudin N. Postpartum depression symptoms in survey-based research: a structural equation analysis. BMC Public Health. 2021;21:27.
[2] Di Florio A, Meltzer-Brody S. Is postpartum depression a distinct disorder? Curr Psychiatry Rep. 2015;17:76.
[3] Stewart DE, Vigod SN. Postpartum depression: pathophysiology, treatment, and emerging therapeutics. Annu Rev Med. 2019;70:183–96.
[4] Kroska EB, Stowe ZN. Postpartum depression: identification and treatment in the clinic setting. Obstet Gynecol Clin North Am. 2020;47:409–19.
[5] Wang K, An N, Jiang X, et al. Comments on the paper by Nielsen et al. entitled “Intraoperative S-ketamine for the reduction of opioid consumption and pain one year after spine surgery: a randomized clinical trial of opioid-dependent patients.” Eur J Pain. 2019;23:1221.
[6] Calvert M, Blazey J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA. 2013;309:814–22.
[7] Molero P, Ramos-Quiroga JA, Martin-Santos R, et al. Antidepressant efficacy and tolerability of ketamine and esketamine: a critical review. CNS Drugs. 2018;32:411–20.
[8] Adams HA, Meyer P, Stoppa A, et al. Anaesthesia for caesarean section. Comparison of two general anaesthetic regimens and spinal anaesthesia. Anaesthesia. 2003;58:23–32.
[9] Wang H, Duan CY, Huang WQ, et al. Perioperative intravenous S(+) ketamine for acute postoperative pain in adults: study protocol for a multicentre, randomised, open-label, positive-controlled, pragmatic clinical trial (SAFE-SK-A trial). BMJ Open. 2021;11:e054681c054681.
[10] Vinsanen H, Liljo T, Sagalajev B, et al. Neurophysiological response properties of medullary pain-control neurons following chronic treatment with morphine or oxycodone: modulation by acute ketamine. J Neurophysiol. 2020;124:790–801.
[11] Brinck ECV, Maisniemi K, Kankare J, et al. Analgesic effect of intraoperative intravenous S-Ketamine in opioid-naive patients after major lumbar fusion surgery is temporary and not dose-dependent: a randomized, double-blind, placebo-controlled clinical trial. Anesth Analg. 2021;122:69–79.
[12] Limandri BJ. Postpartum depression: when the stakes are the highest. J Psychosoc Nurs Ment Health Serv. 2019;57:9–14.
[13] Wszołek K, Żurawska J, Łuczak-Wawrzyniak J, et al. Postpartum depression - a medical or a social problem? J Matern Fetal Neonatal Med. 2020;33:2556–60.
[14] Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: a randomized clinical trial. JAMA Psychiatry. 2018;75:139–48.
[15] Canuso CM, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine for the rapid reduction of symptoms of depression and suicidality in patients at imminent risk for suicide: results of a double-blind, randomized, placebo-controlled study. Am J Psychiatry. 2018;175:620–30.
[16] Kamp J, Jonkman K, van Velzen M, et al. Pharmacokinetics of ketamine and its major metabolites norketamine, hydroxynorketamine, and dehydronorketamine: a model-based analysis. Br J Anaesth. 2020;125:750–61.
[17] Perez-Ruixo C, Rossenu S, Zannikos P, et al. Population pharmacokinetics of esketamine nasal spray and its metabolite noresketamine in healthy subjects and patients with treatment-resistant depression. Clin Pharmacokin. 2021;60:501–16.
[18] Schatzberg AF. Mechanisms of action of ketamine and esketamine. Am J Psychiatry. 2021;178:11301130–1130.
[19] Mihaljević S, Pavlović M, Reiner K, et al. Therapeutic mechanisms of ketamine. Psychiatr Danub. 2020;32:325–33.
[20] Findeis H, Sauer C, Cleare A, et al. Urothelial toxicity of esketamine in the treatment of depression. Psychopharmacology (Berl). 2020;237:3295–302.