Effects of Different Doses of Esketamine on Analgesia and Postpartum Depression after Cesarean Section: Randomized Clinical Trial

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Abstract: Purpose: To evaluate the effects of different esketamine doses on postoperative analgesia and postpartum depression after cesarean section (CS). Methods: In this randomized, double-blind, placebo-controlled trial, 240 singleton parturients (ASA I-II) undergoing elective CS under combined spinal-epidural anesthesia were allocated to four groups: control (C) and three esketamine dose groups (E0.5, E1.0, E1.5) for patient-controlled intravenous analgesia (PCIA). The Edinburgh Postnatal Depression Scale (EPDS) was assessed preoperatively and at 3, 7, and 42 days postoperatively. Pain scores (4 h, 8 h, 12 h, 24 h, and 48 h postoperatively), adverse effects, and exclusive breastfeeding (72 h postoperatively) were recorded. Results: Postoperative analgesia for cesarean deliveries was effective in all four groups, but the E1.0 group showed the best analgesic effect, the lowest incidence of adverse reactions, and the highest breastfeeding rate ($p<0.05$). Postpartum EPDS values were significantly higher than those in prepartum in all four groups ($p<0.05$). Conclusion: Esketamine was safer and more effective in the E1.0 group for PCIA after CS, with the lowest incidence of adverse effects and highest breastfeeding rate.

***Keywords*:** Esketamine; Cesarean section; Postpartum; Analgesia; Depression

1. Introduction

The global average cesarean delivery rate has risen to 21.1% since 2010 and 33.3% in the United States. With the full liberalization of the birth policy, the cesarean section rate is as high as 46% in Chin. Persistent postoperative pain caused by surgical incisions and uterine contractions may lead to postpartum depression (PPD). The incidence of PPD in China is 34.8%, which seriously affects maternal postpartum recovery, family quality of life, and emotional and social cognitive development in infants and children. Therefore, optimal pain management, including good postoperative analgesia and psychotropic drugs after cesarean deliveries, is nowadays receiving great attention[1].

In 2019, the American Society for Promoting Recovery, in conjunction with the Committee on Perioperative Quality Initiatives, stated that multimodal analgesia like N-methyl-D-aspartate (NMDA) receptor antagonists should be considered for perioperative pain management rather than opioids. Ketamine as an NMDA receptor antagonist displays analgesic and anti-maternal PPD effects for patient-controlled intravenous analgesia (PCIA) after cesarean sections (CS). Esketamine, the S-enantiomer of ketamine, a non-competitive NMDA receptor antagonist, is approved by the US Food and Drug Administration (FDA) for treating refractory depression. However, the effects of different doses of esketamine on analgesia and postpartum depression in cesarean section (CS) patients are still unclear[2].

This study aimed to observe the effects of different esketamine doses combined with low-dose sufentanil on PCIA and PPD after CS, to evaluate the efficacy and safety of esketamine injection in such patients, to explore the relative optimal dosage of esketamine, and to provide a clinical reference for improving the prognosis of mothers undergoing cesarean deliveries and optimizing enhanced recovery after surgery (ERAS).

2. Methods

2.1 Study design

This randomised, double-blind, placebo-controlled trial was conducted at the Affiliated Hospital of Jining Medical University in China. This study was approved by the Medical Ethics Committee of the Affiliated Hospital of Jining Medical College (No 2021C150). Written informed consent was obtained from each participant.

2.2 Participants

We enrolled 240 American Society of Anesthesiologists (ASA) I-II pregnant women scheduled for elective CS under combined spinal-epidural anesthesia from September 2021 to October 2023. Exclusion criteria included contraindications to spinal-epidural anesthesia, hypertension and heart diseases, drug allergies, intraoperative bleeding >10 ml/kg or surgery >2

h, and patient withdrawal[3].

2.3 Sample size estimation and statistical analysis

A preliminary experiment with 10 people in each group indicated a 10% reduction in postpartum depression rates at 42 days in E1.0 group. By using PASS 15.0 (NCSS, LLC) with α=0.05 (two-tailed) and 90% power, and accounting for a 10% dropout rate, a minimum of 58 participants per group was required. We enrolled 268 participants, and after excluding 28 lost to follow-up, 60 participants per group were included in the final analysis.

Data were analyzed using SPSS 25.0. Continuous variables following a normal distribution (Shapiro-Wilk test) were compared using ANOVA and are presented as mean ± SD. Categorical variables were analyzed using the chi-square test and are expressed as percentages. A p-value < 0.05 was considered statistically significant[4].

3. Results

3.1 Pre-and intraoperative subject data

A total of 240 participants were equally allocated to four groups (C, E0.5, E1.0, E1.5; n=60 each). No significant differences were observed in age, body mass index (BMI), education, parity, operative time, or intraoperative bleeding among the groups (P>0.05; Table 1).

Table 1. Pre-and intraoperative patient data of the four groups (mean±SD)

Index	Group C (n=60)	Group E0.5 (n=60)	Group E1.0 (n=60)	Group E1.5 (n=60)	F/χ^2	P value
Age (years)	28.2±3.4	27.5±3.3	27.2±3.1	28.2±2.9	1.45	0.228
BMI (kg/m^2)	27.9±2.2	27.7±2.4	28.2±1.9	27.7±2.5	0.58	0.628
Educational level (Bachelor and above/below, cases)	17/43	20/40	15/45	9/51	5.69	0.128
Number of births (1/2/3, cases)	20/31/9	16/36/8	18/34/8	25/27/8	3.79	0.704
Duration of surgery (min)	46.3±6.7	44.2±7.4	45.4±7.3	45.5±8.9	0.751	0.523
Intraoperative bleeding volume (ml)	252.2±25.4	252.3±25.3	253.3±27.7	255.2±26.6	0.165	0.92

Note: Chi-square test was used for education level and production rank, and ANOVA was used for other basic indicators.

3.2 Comparison of postoperative analgesia in four study groups

Postoperative analgesia was effective across all groups. VAS scores at 4–48 h were significantly lower in the E1.0 and E1.5 groups compared to the control group (P<0.05), with the E1.0 group showing the lowest scores (Table 2). The analgesic demand frequency was also lowest in the E1.0 group (Table 3), indicating that 1.0 mg/kg esketamine provided the best analgesic effect in cesarean section patients.

Table 2. Comparison of VAS scores after cesarean delivery in four study groups (mean±SD)

Time point	Group C (n=60)	Group E0.5 (n=60)	Group E1.0 (n=60)	Group E1.5 (n=60)	F	P value
4 h postoperatively	2.33±0.68▲	1.98±0.85*▲	1.48±0.79*	1.82±0.68*▲	13.188	0.001
8 h postoperatively	2.67±0.73▲	2.45±0.93▲	1.63±0.55*	2.33±0.71*▲	21.844	0.001
12 h postoperatively	2.55±0.72▲	2.32±1.02▲	1.78±0.56*	2.15±0.68*▲	10.705	0.001
24 h postoperatively	2.22±0.64▲	1.75±0.82*▲	1.30±0.46*	1.68±0.65*▲	19.816	0.001
48 h postoperatively	1.68±0.50▲	1.38±0.67*▲	1.07±0.61*	1.35±0.61*▲	10.649	0.001

*Compared with group C, P<0.05

▲Compared with E1.0 group, P<0.05

Compared with the control group, * means p<0.05; Compared with the Group E1.0 # means p<0.05.

Table 3. Comparison of analgesia frequency after cesarean delivery in four study groups (mean±SD)

Groups	Group C (n=60)	Group E0.5 (n=60)	Group E1.0 (n=60)	Group E1.5 (n=60)	F	P value
Analgesia frequency	2.68±2.63▲	1.87±1.71*▲	0.80±1.54*	1.53±1.56*▲	10.019	0.001

* Compared with group C, P<0.05

▲ Compared with E1.0 group, P<0.05

3.3 Comparison of EPDS scores among the four study groups

The effects of different esketamine doses on postpartum depression were assessed using EPDS scores. Preoperative scores did not differ significantly among groups ($p>0.05$). Postpartum scores increased significantly compared to preoperative values in all groups ($p<0.05$), but no significant differences were observed between the esketamine groups and the control group at 3, 7, or 42 days postpartum ($p>0.05$). A trend of dose-dependent reduction in EPDS scores was noted, with the lowest scores in the E1.5 group, although this did not reach statistical significance (Table 4).

Table 4. Comparison of EPDS scores pre-and postoperatively in the four groups (mean±SD)

Time point	Group C (n=60)	Group E0.5 (n=60)	Group E1.0 (n=60)	Group E1.5 (n=60)	F	P value
Before delivery	4.40±2.20	4.45±2.61	4.38±2.45	4.52±2.99	0.032	0.992
3 days after delivery	6.73±3.85*	6.38±3.78*	6.00±3.99*	5.80±3.28	0.738	0.530
7 days after delivery	6.93±4.43*	6.67±3.64*	6.13±4.21*	5.98±3.40*	0.769	0.513
42 days after delivery	7.10±4.29*	6.75±4.22*	6.50±4.12*	6.18±4.24*	0.508	0.677

*Compared with prenatal values, $p<0.05$.

3.4 Comparison of postoperative adverse effects in all four groups

Table 5. Occurrence of adverse reactions in each group[cases (%)]

Adverse reaction	Group C (n = 60)	Group E0.5 (n = 60)	Group E1.0 (n = 60)	Group E1.5 (n = 60)	$\chi 2$	P value
Vertigo	36 (60%)	25 (42%)	9 (15%)	13 (22%)	33.060	0.001
Nausea	23 (38%)	17 (28%)	9 (15%)	11 (18)	10.667	0.014
Vomiting	16 (27%)	14 (23%)	8 (13%)	10 (17%)	4.167	0.244
Headache	12 (20%)	11 (18%)	8 (13%)	10 (17%)	1.030	0.794

Postoperative adverse effects were summarized in Table 5. No complications such as diplopia, hallucinations, or myalgias occurred in any group. The incidence of vertigo and nausea was significantly lower in the esketamine groups compared to the control group ($p<0.05$), whereas vomiting and headache did not differ significantly. The E1.0 group exhibited the lowest overall incidence of adverse reactions, suggesting that 1.0 mg/kg esketamine most effectively reduced postoperative side effects.

3.5 Comparison of exclusive breastfeeding at 72 h after surgery in the four groups

Table 6. Exclusive breastfeeding at 72 h after surgery in each group[cases (%)]

Groups	Group C (n = 60)	Group E0.5 (n = 60)	Group E1.0 (n = 60)	Group E1.5 (n = 60)	$\chi 2$	P value
Exclusive breastfeeding	26 (43%)	38 (63%)	46 (77%)	31 (52%)	15.594	0.001

The exclusive breastfeeding rate was significantly higher in the E0.5 and E1.0 groups compared to the control group ($p<0.05$; Table 6), indicating that esketamine at 0.5 or 1.0 mg/kg could increase the rate of exclusive breastfeeding post-cesarean section.

4. Discussion

Postpartum depression is a common complication occurring within weeks after delivery. EPDS is a widely recommended tool for postpartum mood assessment. In line with Chinese expert consensus, we used an EPDS score ≥9 as the screening threshold for PPD at 3, 7, and 42 days postpartum. Cesarean delivery is a known independent risk factor for PPD . Of 268 initially screened patients, 240 (89.6%) completed the study. Compared to prenatal period, all participants showed varying elevated EPDS scores postoperatively, supporting CS as a major risk factors for PPD.

Chronic pain and depression are recognized to share common pathophysiological mechanisms. Effective postpartum analgesia may therefore help mitigate the risk of PPD. PCIA is widely used after cesarean delivery for its efficacy and convenience. While opioids remain a mainstay of PCIA, their use is associated with side effects including dizziness, nausea, and vomiting. In our study, although analgesia was adequate in the control group, the incidence of these adverse reactions was significantly higher compared to groups receiving low-dose sufentanil combined with esketamine..

Esketamine is an S-enantiomer of ketamine that dispenses effective analgesia, primarily mediated through NMDA receptor antagonism, thus, resulting in reduced central sensitization. It also modulates the pain threshold and reduces post-anesthetic nociceptive sensitization. Although all four medication groups received the required post-CS analgesia, the VAS score values of E1.0 and E1.5 groups were lower than the control group. The E1.0 group displayed the best analgesic effect with the least adverse reactions and a relatively high breastfeeding rate at 3 days postpartum.

Esketamine may produce antidepressant effects via AMPA receptor activation and increased BDNF synthesis. Previous studies revealed 1.5 mg/kg esketamine significantly reduced EPDS scores at 42 days post operation. Our study observed a similar reduction without statistical significance, possibly due to lower drug exposure, limited sample size, or later assessment time points. Singh et al. revealed that esketamine (0.20 mg/kg and 0.40 mg/kg) was significantly effective 2 h after intravenous infusion (the earliest time point measured). Esketamine blood levels were much lower in our study, and depression was observed for a relatively long time (most recently, 3 days after dosing), so the antidepressant effect was not significant. Future studies can explore in depth the minimum dose and time frame for esketamine to exert its antidepressant effects, and provide a reference for the safe and effective clinical application of esketamine for post-CS analgesia.

5. Conclusions

In conclusion, while postpartum EPDS scores increased significantly across all groups, the use of 1.0 mg/kg esketamine (E1.0 group) provided safer and more effective postoperative analgesia. This regimen was associated with the lowest incidence of adverse effects, the highest rate of exclusive breastfeeding, and showed a potential early (within 7 days) positive trend on maternal mood scores.

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Trial registration

Chinese Clinical Trial Registry (ChiCTR2100053376 (2021/11/20). http://www.chictr.org.cn/index.aspx.

References

[1] Antoine C and Young BK. Cesarean section one hundred years 1920-2020: the Good, the Bad and the Ugly. J Perinat Med. 2020,(56):5-16.

[2] Betran AP, Ye J, Moller AB, Souza JP and Zhang J. Trends and projections of caesarean section rates: global and regional estimates. BMJ Glob Health. 2021,(6):98-102.

[3] Jadon A, Jain P, Chakraborty S, Motaka M, Parida SS, Sinha N, Agrawal A and Pati AK. Role of ultrasound guided transversus abdominis plane block as a component of multimodal analgesic regimen for lower segment caesarean section: a randomized double blind clinical study. BMC Anesthesiol. 2018,(18):53-59.

[4] Wang Z, Liu J, Shuai H, Cai Z, Fu X, Liu Y, Xiao X, Zhang W, Krabbendam E, Liu S, Liu Z, Li Z and Yang BX. Mapping global prevalence of depression among postpartum women. Transl Psychiatry. 2021,(11):543-556.