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Original Article

The effect of an intravenous analgesic pump with esketamine on postoperative pain and postpartum depression in women with cesarean section

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Abstract: Objective: This study aims to investigate the efficacy of an intravenous analgesic pump containing esketamine for postoperative pain relief and its impact on postpartum depression in women undergoing cesarean sections. Methods: A retrospective analysis was conducted on 147 women who underwent cesarean deliveries at Xiamen Hospital of Traditional Chinese Medicine from April 2022 to May 2024. Based on different pain management protocols, the participants were divided into two groups: the observation group (n=81) and the control group (n=66). The observation group received intravenous esketamine post-delivery, followed by postoperative analgesia using a pain pump with esketamine and Sufentanil. Various outcomes were assessed, including Visual Analog Scale (VAS) pain scores, Edinburgh Postnatal Depression Scale (EPDS) scores, and serum levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), cortisol (Cor), and brain-derived neurotrophic factor (BDNF). Results: At 12, 24, and 48 hours post-surgery, VAS pain scores (both resting and coughing) were significantly lower in the observation group compared to the control group (P<0.05). EPDS scores were significantly higher at 3, 7, and 42 days post-surgery in both groups compared to pre-surgery levels (P<0.05), with the observation group exhibiting significantly lower EPDS scores at 3 and 7 days (P<0.05). Serum levels of IL-6, TNF-α, and Cor were significantly reduced at 24 and 48 hours post-surgery in both groups, while BDNF levels were significantly elevated (P<0.05). At 24 and 48 hours, the observation group had significantly lower levels of IL-6, TNF-α, and Cor, along with higher BDNF levels, compared to the control group (P<0.05). No significant differences in adverse reactions were observed between the two groups (P>0.05). Conclusion: Esketamine-based postoperative analgesia for cesarean section effectively reduces perioperative pain, alleviates postpartum depression, mitigates inflammatory and stress responses, and has certain neuroprotective effects. Its safety profile supports its potential for broader clinical use.

Keywords: Esketamine, intravenous analgesia, caesarean section, postpartum pain, postpartum depression

Introduction

Cesarean section (C-section), a surgical procedure involving an incision in the mother's uterus to deliver the fetus, is commonly used in obstetric practice to manage various complications during childbirth [1]. However, due to factors such as the surgical incision and uterine contractions, women undergoing C-sections are at high risk for significant postoperative pain, which triggers a strong stress response. This pain not only impedes physical recovery but can also lead to psychological distress, increasing the likelihood of developing postpartum depression [2]. Studies have shown that the incidence of postpartum depression remains high, influenced by a range of factors including genetic predisposition, environmental conditions, family dynamics, and social support [3]. Postpartum depression typically emerges within the first four weeks after delivery, with incidence rates ranging from 15% to 40%. While many women recover spontaneously within three to six months, severe cases can persist for one to two years, significantly impacting maternal health, infant development, and family well-being, with broader societal repercussions [4, 5]. Actively preventing and treating postpartum depression is essential for improving the quality of life for postpartum women,

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fostering a supportive family environment for newborns, and reducing suicide risk among mothers with depression. Furthermore, it contributes to overall family well-being [6]. Ketamine, a well-established N-methyl-D-aspartate (NMDA) receptor antagonist, has long been recognized for its significant role in both intraoperative and postoperative analgesia. It is a key component of multimodal analgesic regimens in clinical practice [7, 8]. In addition to its potent analgesic properties, ketamine also exhibits sedative, anti-inflammatory, and antidepressant effects. However, its use is associated with adverse effects such as hallucinations, persistent nightmares, and the risk of extrapyramidal symptoms, leading to its gradual replacement by newer opioid alternatives since the 1990s. Esketamine, the S-enantiomer of ketamine, shares a similar mechanism of action. It primarily exerts its effects by noncompetitively inhibiting NMDA receptor activation by glutamate through binding to the phenylpiperidine site. The blockade of NMDA receptors is both time- and frequency-dependent, resulting in reduced neuronal activity and subsequent anesthetic and analgesic effects [9]. Compared to ketamine, esketamine demonstrates stronger anesthetic and analgesic effects, fewer mental side effects, less secretion, shorter recovery times, and notable antidepressant properties [10]. Given its sedative and antidepressant effects, esketamine shows promise for use in obstetric analgesia, offering pain relief while potentially alleviating postpartum depression. However, research in this area remains limited, and further clinical investigations are needed. This study explores the impact of an esketamine intravenous analgesia pump on postoperative pain and postpartum depression in mothers undergoing C-sections, with findings reported as follows.

Materials and methods

Clinical data

This retrospective study included 147 women who underwent C-sections at our institution between April 2022 and May 2024. Participants were stratified into two groups based on different postoperative analgesia protocols: the observation group (n=81) and the control group (n=66). Ethical approval for this study was granted by the ethics committee of our hospital.

Inclusion and exclusion criteria

Inclusion criteria: ① Age between 22 and 35 years; ② Singleton intrauterine pregnancy, with gestational age between 37 and 41 weeks; ③ Indication for C-section delivery, as per established guidelines [11], with an ASA classification of I or II; ④ No history of severe pregnancy complications; ⑤ Normal fetal heart rate monitoring before surgery; ⑥ Stable mental status before surgery, with no history of depression.

Exclusion criteria: ① A history of allergy to esketamine, fentanyl, or other related drugs; ② A history of opioid addiction; ③ Coagulation dysfunction; ④ Liver or kidney dysfunction; ⑤ Use of opioids or central nervous system medications within 14 days before surgery; ⑥ Diagnosed autoimmune diseases or connective tissue disorders; ⑦ History of neurological or psychiatric disorders.

Methods

Both groups of parturients underwent C-section delivery, with comprehensive preoperative examinations and related preparations. All patients were instructed to fast for 8 hours and withhold fluids for 4 hours prior to the procedure. Upon arrival in the operating room, vital signs were closely monitored, and peripheral venous access was established. Combined spinal-epidural anesthesia was then administered. The anesthesiologist positioned the parturient in the left lateral position, selecting the puncture site at the L2-L3 intervertebral space. The puncture site and surrounding skin were disinfected, and the puncture was performed following standard procedures. A 100 mg dose of 1% ropivacaine hydrochloride (Kerun Pharmaceutical Co., Ltd. Hunan, China, H202-34345) was mixed with 100 ml of 0.9% sodium chloride solution to prepare a 1.2 mL injection, which was administered over 30 seconds. Subsequently, an epidural catheter was inserted into the epidural space. The parturient was then repositioned into a left-tilted supine position, and the anesthesia level was adjusted to T6. If the desired level of anesthesia was not achieved within 5 minutes, an additional dose of 200 mg of 2% lidocaine hydrochloride (prepared in 100 mL of 0.9% sodium chloride solution, with a final volume of 3-5 mL) was administered. The parturient's position was adjusted as necessary, and supplemental oxygen was

provided at a flow rate of 2-5 L/min. Surgical intervention commenced once the anesthesia level reached T6. Throughout the operation, the patient's vital signs were closely monitored. If the systolic blood pressure decreased by more than 20% from baseline, ephedrine hydrochloride (China Huarun Shuanghe Pharmaceutical Co., Ltd., H110205) was administered intravenously as needed. Fifteen minutes before the conclusion of surgery, 0.4 mg/kg midazolam (Yichang Renfu Pharmaceutical Co., Ltd., H20237070) was slowly injected intravenously over 30 seconds. Following surgery, both groups of patients received patient-controlled intravenous analgesia (PCIA) for postoperative pain management.

Observation group: Following the delivery of the fetus, a dose of 0.25 mg/kg of esketamine hydrochloride (China Jiangsu Hengrui Pharmaceutical Co., Ltd., H20193336) was administered intravenously, diluted with 2 mL of sterile water for injection. Postoperative analgesia was provided with esketamine at 1 mg/kg, sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., H20054172) at 2 μg/kg, flurbiprofen axetil (Beijing Ted Pharmaceutical Co., Ltd., H20041508) at 200 mg, and palonosetron (Xiansheng Pharmaceutical Co., Ltd., H2010-0096) at 0.5 mg.

Control group: Postoperative analgesia was achieved without esketamine, while the rest was the same as in the observation group. The PCIA background infusion rate was set to 2 mL/h, with an initial loading dose of 3 mL. The analgesic pump allowed for a single bolus injection of 0.5 mL, with a lockout interval of 15 minutes. The analgesic pump was used for a duration of 48 hours.

Observation indicators

Postoperative pain assessment: Pain levels were evaluated at 6, 12, 24, and 48 hours after surgery, both at rest and during coughing. The Visual Analog Scale (VAS) was used, where mothers rated their pain on a scale from 0 to 10, with 0 representing no pain and 10 indicating the most severe pain. A higher score indicates greater severity of postpartum pain [12].

Postpartum depression scoring: Postpartum depression was assessed using the Edinburgh Postnatal Depression Scale (EPDS) [13] at four time points: pre-surgery, and 3, 7, and 42 days post-surgery. The EPDS consists of ten items assessing the mother's psychological state, with each item scored from 0 to 3 points, yielding a total score of 30 points. An EPDS score of ≥10 points was considered indicative of postpartum depression, with higher scores indicating more severe depression.

Comparison of serum biomarkers: Blood samples (5 mL) were collected from the peripheral veins of participants in both groups at the end of surgery, and at 24 and 48 hours postoperatively. After centrifugation to separate the serum, levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), cortisol (Cor), and brain-derived neurotrophic factor (BDNF) were measured using enzyme-linked immunosorbent assay (ELISA) kits (Abcam, UK; ab178013, ab181421, ab108665, ab212166).

Adverse reactions: The occurrence of adverse reactions was recorded within 48 hours post-surgery in both groups. Reactions of interest included nausea and vomiting, hypotension, drowsiness, and hallucinations.

Newborn Apgar Scores: Apgar scores were recorded for all newborns in both groups at 1 minute and 5 minutes after birth [14].

Statistical analysis

Statistical analyses were performed using SPSS 27.0 software. The measured data were expressed as ($\bar{X} \pm s$), and comparisons of the measured data were conducted using a t-test. For the analysis of quantitative data across multiple time points between groups, repeated measures analysis of variance was employed. Qualitative data were represented as percentages, and comparisons of qualitative data were conducted using the chi-square test. A difference was deemed statistically significant at $P<0.05$. The sample size calculation was based on the formula $n = z^2\sigma^2/d^2$, where Z represents the confidence interval, n denotes the sample size, d indicates the margin of sampling error, and σ signifies the standard deviation, which was determined by aggregating the number of patients admitted to our hospital.

Results

Comparison of clinical data

There were no statistically significant differences in age, BMI, gestational age, ASA classifica-

Table 1. Comparison of clinical data between the two groups

Clinical data	Observation Group (n=81)	Control group (n=66)	t/x^2	*P*
Age (years, $\bar{x}\pm s$)	29.30±3.16	29.89±2.69	1.203	0.231
BMI (kg/m^2, $\bar{x}\pm s$)	27.52±2.47	27.83±2.72	0.723	0.471
Eestational week (week, $\bar{x}\pm s$)	39.40±1.65	38.95±1.79	1.583	0.116
ASA Classification				
I	21	15	0.201	0.654
II	60	51		
Operation time (min, $\bar{x}\pm s$)	64.62±10.54	62.27±11.83	1.273	0.205
Blood loss during surgery (ml, $\bar{x}\pm s$)	289.50±72.19	275.69±68.53	1.180	0.240
Educational level				
High school or below	25	18	0.227	0.634
Bachelor's degree or higher	56	48		

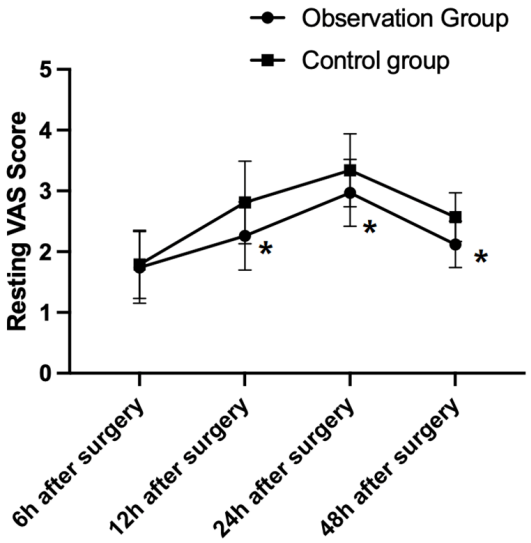

Figure 1. A comparison of postoperative resting pain levels between the two groups. Note: Compared with the control group, *P<0.05.

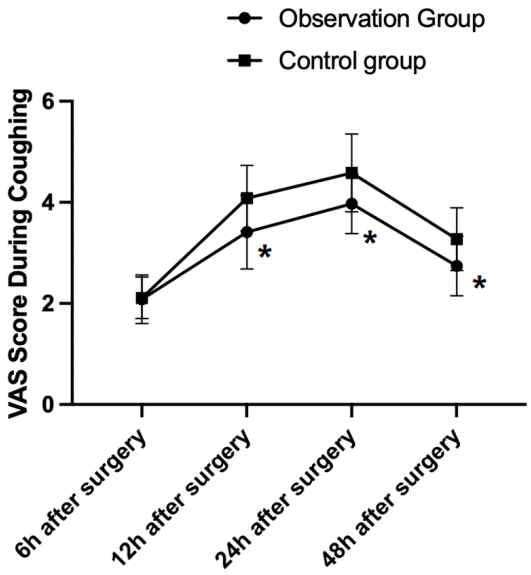

Figure 2. A comparison of the degree of postoperative cough-induced pain between the two groups. Note: Compared with the control group, *P<0.05.

tion, operation time, intraoperative blood loss, or educational level between the two groups (P>0.05), as shown in **Table 1**.

Comparison of postoperative pain levels

No significant differences were observed in the VAS pain scores between the two groups of postpartum women at rest and during coughing 6 hours after surgery (P>0.05). However, at 12, 24, and 48 hours post-surgery, the VAS pain scores at rest and during coughing in the observation group were significantly lower than those in the control group (P<0.05), as shown in **Figures 1** and **2**.

Comparison of postpartum depression severity

The EPDS scores for both groups were significantly elevated at 3 days, 7 days, and 42 days after surgery in comparison to pre-surgery scores (P<0.05). Notably, the observation group exhibited significantly lower EPDS scores at both 3 and 7 days after surgery compared to the control group (P<0.05), as shown in **Figure 3**.

Comparison of serum biomarkers

Serum levels of IL-6, TNF-α, and Cor were significantly reduced at 24 and 48 hours after sur-

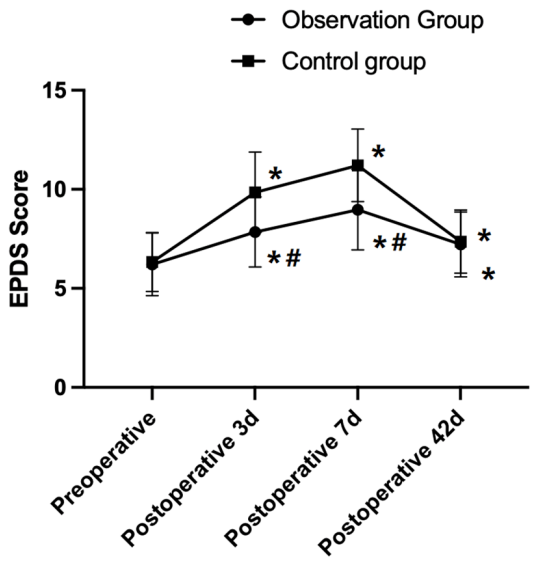

Figure 3. Scores of postpartum depression levels for the two groups. Note: Compared with the group before surgery, *P<0.05; compared with the control group of the same period, #P<0.05.

gery in both groups, compared to preoperative levels (P<0.05). However, BDNF levels were significantly higher at these time points (P<0.05). The observation group had significantly lower levels of IL-6, TNF-α, and Cor, as well as significantly higher levels of BDNF compared to the control group at 24 and 48 hours post-surgery (P<0.05), as shown in **Figure 4**.

Comparison of adverse reactions

In the observation group, there were 2 cases of nausea and vomiting, 4 cases of hypotension, 1 case of drowsiness, and 1 case of hallucination, resulting in an adverse reaction rate of 11.11%. In the control group, 3 cases of nausea and vomiting, 2 cases of hypotension, and 3 cases of drowsiness occurred, yielding an adverse reaction rate of 12.12%. No significant differences in adverse reaction rates between the two groups were observed (P>0.05), as shown in **Table 2**.

Comparison of Apgar scores between two groups of newborns

There were no significant differences in the 1-minute and 5-minute Apgar scores between the two groups of newborns (P>0.05), as shown in **Table 3**.

Discussion

Esketamine, an isomer of ketamine, is known for its potent analgesic properties and significant antidepressant effects. C-section is a major obstetric surgical procedure, which places significant physiological stress on women. This stress, combined with the changes associated with surgery, often challenges the maintenance of a stable psychological state, contributing to an increased incidence of postpartum depression [15]. Factors related to surgical trauma, including the incision and uterine contractions, contribute to moderate to severe postoperative pain, which can negatively impact physical recovery, breastfeeding, and early mother-infant bonding. Furthermore, unaddressed pain after C-section is strongly linked with a higher risk of psychological disorders, such as postpartum anxiety and depression [16, 17]. Therefore, the objective of this study is to investigate the effects of an intravenous analgesia pump using esketamine on postoperative pain and postpartum depression in women after cesarean delivery. Through this research, we seek to establish a foundation for the clinical application of esketamine in this population.

Moderate to severe postoperative pain in C-section patients is closely associated with reduced physical activity. The intensity of pain is inversely correlated with the level of postoperative mobility, which in turn extends the recovery period, increases the length of hospital stay, and raises medical costs [18, 19]. Pain acts as a trigger for sympathetic nervous system activation, which results in increased oxygen consumption and exacerbates the body's stress response. This physiological response leads to emotional disturbances in the mother, including irritability, anxiety, and depression [20, 21]. Upon receiving pain signals, the body initiates the stress response, resulting in the release of neurotransmitters that further elevate oxygen consumption. Concurrently, pain signals are transmitted to the cerebral cortex, which affects the hypothalamic-pituitary axis. This interaction results in diminished prolactin secretion, reduced lactation, and compromised capacity for infant feeding [22, 23].

Severe pain stimulation has a profound impact on both the psychological and physiological

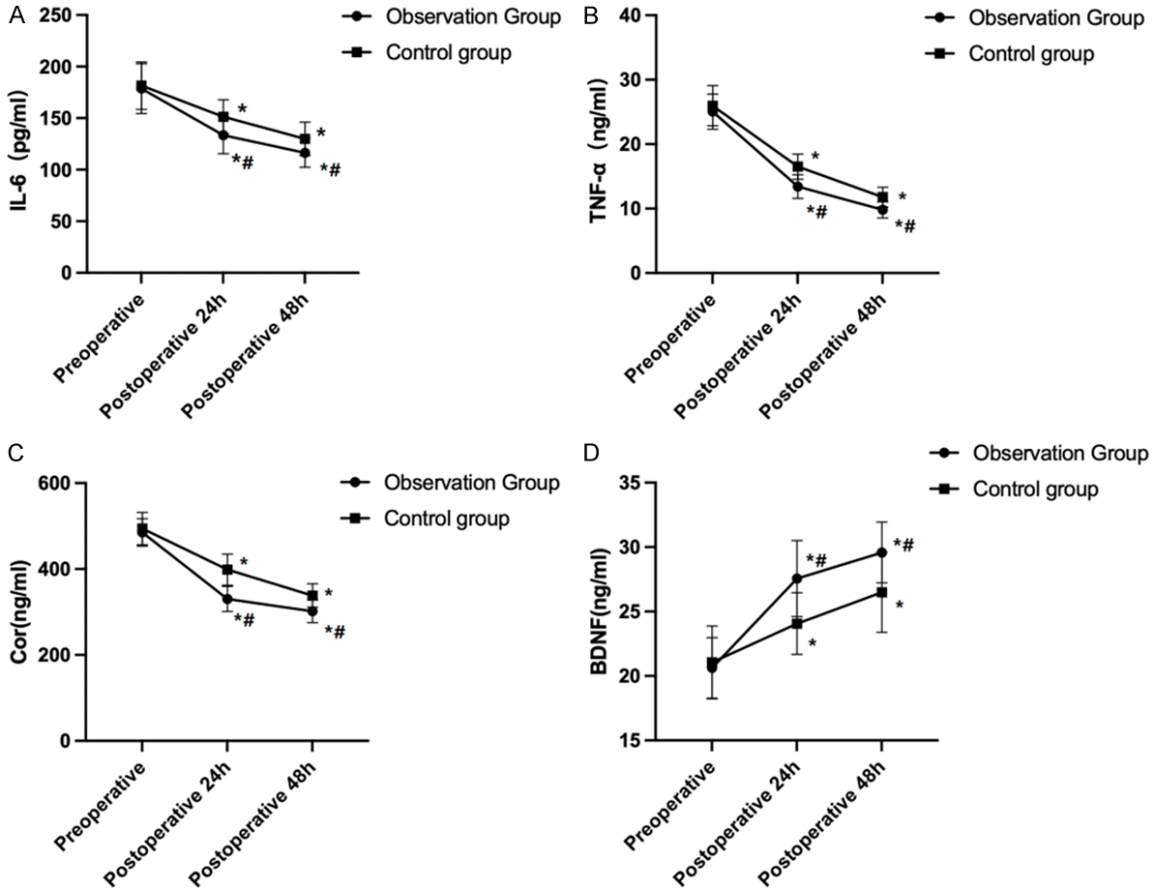

Figure 4. Comparison of serum indicators between the two groups of postpartum women. Note: Compared with the group before surgery, *P<0.05; compared with the control group of the same period, #P<0.05.

Table 2. Comparison of adverse reactions between two groups [n (%)]

Group	n	Nausea and vomiting	Low blood pressure	Drowsiness	Hallucination	Total
Observation Group	81	2 (2.47)	4 (4.94)	1 (1.23)	1 (1.23)	9 (11.11)
Control group	66	3 (4.54)	2 (3.03)	3 (4.54)	0 (0.00)	8 (12.12)
x^2	-	-	-	-	-	0.036
P	-	-	-	-	-	0.489

Table 3. Comparison of Apgar scores between two groups of newborns

Group	N	1 min after birth	5 min after birth
Observation group	81	9.17±0.26	9.56±0.17
Control group	66	9.09±0.29	9.51±0.15
t	-	1.762	1.869
P	-	0.080	0.064

responses of postpartum women. The pain response leads to dysfunction of the autonomic nervous system, and there is a positive correlation between the intensity of pain and the severity of anxiety and depressive symptoms. This, in turn, significantly affects the mother's mood, sleep, and overall well-being [24, 25]. Approximately 30% of women undergoing C-sections experience significant postoperative pain, which substantially prolongs recovery. Pain-related stress responses induce the release of stress hormones (such as adrenaline and glucocorticoids), which negatively affect uterine contractions and gastrointestinal motility [26, 27]. Thus, effective and safe postoperative pain management is crucial, not only

to facilitate the recovery of physical function but also to alleviate the psychological burdens of anxiety and depression.

The results of this study show that, at 12, 24, and 48 hours post-surgery, the VAS pain scores for both resting and coughing in the observation group were significantly lower than those in the control group. These findings are consistent with previous research, which has shown that esketamine is effective in alleviating postoperative pain in C-section patients [28, 29]. Esketamine exerts its analgesic effects through multiple mechanisms, primarily by blocking NMDA receptors on both pre- and post-synaptic neurons, thereby disrupting the pain transmission pathway. Additionally, esketamine interacts with central opioid receptors to enhance analgesia. Notably, esketamine has a high affinity for NMDA receptors, and its analgesic potency is superior to that of ketamine. When used in combination with opioids, esketamine produces a synergistic effect, thereby enhancing the overall analgesic efficacy of opioids [30, 31]. At 3, 7, and 42 days after surgery, both groups exhibited significantly higher EPDS scores compared to preoperative level. However, the observation group showed significantly lower EPDS scores than the control group at both 3 and 7 days post-surgery. These findings suggest that mothers experience a marked increase in depressive symptoms following C-section, likely due to hormonal fluctuations and postoperative pain. However, the administration of esketamine appears to effectively mitigate postpartum depression, demonstrating substantial antidepressant properties. Furthermore, at 24 and 48 hours following surgery, serum levels of IL-6, TNF-α, and Cor were significantly reduced in both groups compared to pre-surgery levels. In contrast, BDNF levels were significantly elevated. Notably, at the same time points, the observation group had significantly lower serum levels of IL-6, TNF-α, and Cor, along with significantly higher BDNF levels compared to the control group. These results indicate that esketamine administration for postoperative pain management in C-section patients can effectively reduce the inflammatory response (as indicated by IL-6 and TNF-α), modulate the stress response (as reflected by Cor levels), and provide neuroprotective benefits (evidenced by increased BDNF levels).

It is important to note that the relatively small sample size in this study, may introduce some bias, and future studies with larger sample sizes are necessary to confirm these findings and improve the reliability of the clinical data. In summary, esketamine administration for postoperative analgesia following C-section has been shown to effectively reduce perioperative pain, alleviate postpartum depression, and mitigate postoperative inflammatory and stress responses. Furthermore, esketamine demonstrates neuroprotective effects, making it a promising candidate for clinical use in this setting, especially given its favorable safety profile.

Disclosure of conflict of interest

None.

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