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Epidural Esketamine Relieves Postoperative Pain, Suppresses Perioperative Inflammation and Mitigates Postpartum Depression Following Cesarean Delivery: A Randomized Controlled Trial

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Abstract

Background Cesarean section frequently leads to moderate-to-severe postoperative pain, enhanced perioperative inflammation and increased incidence of postpartum depression. Esketamine possesses analgesic, anti-inflammatory and psychotropic effects via inhibiting NMDA receptors. Although intravenous esketamine is commonly used for obstetric analgesia, the clinical value of epidural esketamine after cesarean delivery requires further verification. This study aims to evaluate the impacts of epidural esketamine on postoperative pain intensity, perioperative inflammatory indicators, postpartum depression and safety in cesarean section patients.

Methods Eighty parturients scheduled for cesarean section under neuraxial anesthesia were randomly assigned to control group (Group C) and esketamine group (Group T) using a random number table method, with 40 patients in each group. All parturients received postoperative patient-controlled intravenous analgesia (PCIA). Before skin closure, each patient received a 5 mL epidural injection of the assigned study drug. Group C received 5 mL normal saline, and Group T received 0.2 mg/kg esketamine diluted to 5 mL. Resting Numerical Rating Scale (NRS) pain scores were recorded at 2, 6, 12, 24 and 48 h postoperatively. Dynamic pain and uterine contraction pain NRS scores, as well as the number of PCIA bolus requests, were documented at 24 h and 48 h after surgery. Venous blood samples were collected before and one day after surgery to measure serum cortisol, C-reactive protein (CRP) and interleukin-6 (IL-6) for evaluation of perioperative inflammatory status. The Edinburgh Postnatal Depression Scale (EPDS) was administered 1 day before operation, 1 week and 6 weeks after delivery to assess depressive symptoms and the incidence of postpartum depression. The incidences of adverse reactions including postoperative nausea and vomiting, pruritus and shivering, as well as psychiatric adverse reactions such as dizziness, drowsiness, irritability and emotional excitement, were recorded.

Results Compared with Group C, Group T exhibited significantly lower resting NRS scores from 2 h to 48 h postoperatively, lower dynamic pain and uterine contraction pain NRS scores at 24 h and 48 h, and fewer rescue analgesia requirements within 48 h (all $P < 0.05$). Preoperative serum cortisol, CRP and IL-6 levels were comparable between the two groups ($P > 0.05$). At 24 h postoperatively, serum cortisol, CRP and IL-6 concentrations in Group T were markedly lower than those in Group C ($P < 0.05$). EPDS scores and the positive screening rate of postpartum depression at postoperative 1 week and 6 weeks were significantly lower in Group T ($P < 0.05$). The incidences of postoperative nausea and vomiting, pruritus and shivering were similar between the two groups ($P > 0.05$). The rates of psychiatric adverse events including dizziness, drowsiness, irritability, excitement and blurred vision were slightly higher in Group T, without statistically significant intergroup differences ($P > 0.05$).

Conclusion Single epidural administration of 0.2 mg/kg esketamine prior to skin closure enhances postoperative pain relief, suppresses perioperative inflammation, and alleviates postpartum depressive symptoms after cesarean section. The incidence of mild psychiatric side effects was slightly higher but not statistically significant. Epidural esketamine appears to be a safe adjuvant analgesic for parturients receiving cesarean delivery.

Trial registration Chictr.org.cn identifier ChiCTR2400090341 (Date of registry: 27/09/2024, Retrospectively registered).

Background

Cesarean section constitutes a core surgical modality for managing high-risk pregnancy, dystocia and other obstetric complications in clinical practice. The global cesarean delivery rate has been steadily rising, with approximately one-fifth of all births currently accomplished via cesarean section; this proportion reaches as high as one-third in high-income countries including the United Kingdom, the United States and Australia[1]. Postoperative pain and postpartum depression represent the two most prevalent and interrelated complications during the perioperative period of cesarean section. They markedly compromise maternal physical rehabilitation, emotional status and mother-infant quality of life, and have emerged as critical concerns in the fields of obstetric anesthesia and perinatal healthcare.

Postpartum pain following cesarean section is predominantly characterized by incisional resting pain, movement-evoked pain and uterine contraction pain. Inadequate pain control not only hinders early postoperative recovery, but also elevates the risk of postpartum emotional disorders. Surgical trauma, incisional pain and uterine cramping activate systemic stress responses and trigger disordered inflammatory stress, resulting in abnormal elevations of stress and inflammatory biomarkers such as cortisol and interleukin-6. These alterations exacerbate postoperative pain[2, 3], prolong recovery duration, and substantially increase the risk of diverse adverse postoperative events[4].

Postpartum depression is the most common psychological complication among women undergoing cesarean delivery. It typically develops within weeks to months after childbirth, with a widely variable incidence of 11%–20% across regions and postpartum timeframes[5, 6]. Without timely intervention, postpartum depression may lead to impaired family functioning, increased risks of child maltreatment and neglect, infant developmental delay, perinatal obstetric complications, obstacles to breastfeeding, and substantial healthcare costs[7]. Existing studies have confirmed that severe or persistent postoperative pain after cesarean section is an established risk factor for postpartum depression[8–10], highlighting the vital importance of effective postoperative analgesia. Meanwhile, excessive perioperative inflammatory stress may precipitate and aggravate postpartum depression. Evidence indicates that circulating IL-1β and IL-6 levels are positively correlated with the severity of depressive symptoms from gestation through the postpartum period[11]. Accordingly, identifying a well-tolerated adjuvant anesthetic regimen that simultaneously optimizes postoperative analgesia, suppresses perioperative inflammatory stress, and improves maternal postpartum psychological status has become a research priority in obstetric anesthesia.

Esketamine acts as a noncompetitive antagonist of the N-methyl-D-aspartate receptor (NMDAR). Its primary pharmacological mechanism relies on NMDAR blockade to exert analgesic, anti-hyperalgesic and antidepressant effects[12, 13]. Current clinical investigations of esketamine predominantly focus on intravenous administration. By contrast, epidural administration enables direct action on regional nerves

at the surgical site, conferring superior targeted analgesia. Previous research demonstrates that ketamine exerts spinal local anesthetic and analgesic effects with minimal systemic impacts[14, 15]. Nevertheless, clinical studies investigating single-dose epidural esketamine for cesarean section remain scarce. Sufficient clinical data are lacking to clarify its effects on multidimensional postoperative pain, perioperative inflammatory cytokine concentrations, the incidence of postpartum depression, and drug safety in parturients.

On this basis, the present study enrolls parturients undergoing elective cesarean section under neuraxial anesthesia. We aim to explore the impacts of single epidural esketamine administration on maternal pain intensity at different postoperative time points, perioperative inflammatory stress markers, and the occurrence of postpartum depression, together with systematic observation of postoperative adverse reaction profiles. This study intends to provide clinical evidence for optimizing multimodal perioperative analgesia protocols and improving the physical and psychological recovery quality of women after cesarean delivery.

Methods

Study design

This study is a prospective, randomized controlled trial and was approved by the Ethics Committee of Ningbo Medical Center Lihuili Hospital. (Approval No.: KY2024SL110-01). The trial was registered at www.chictr.org.cn (ChiCTR2400090341) before participants were enrolled. This prospective randomized controlled trial was conducted and reported in accordance with the CONSORT guidelines. A total of 88 parturients scheduled for cesarean section under neuraxial anesthesia at Ningbo Medical Center Lihuili Hospital from October 2024 to May 2025 were enrolled after the patient or family agreed and signed an informed consent form.

Inclusion Criteria: (1) Singleton term pregnancy; (2) aged 20–38 years; (3) American Society of Anesthesiologists (ASA) physical status □–□; (4) body mass index (BMI) ≤ 30 kg/m²; (5) intact communication and comprehension ability before surgery, capable of independently completing scale assessments and postoperative follow-up.

Exclusion Criteria: (1) High-risk pregnancy complications including multiple gestation, placenta previa, placental abruption, severe preeclampsia; (2) contraindications to neuraxial anesthesia, such as coagulation disorders, infection at the puncture site, spinal deformity, elevated intracranial pressure, etc.; (3) history of abuse, allergy or contraindication to ketamine, esketamine or opioid analgesics; (4) severe dysfunction of the heart, lung, liver or kidney; (5) preoperative obvious anxiety, depression or a history of psychiatric disorders.

Exclusion from Study: (1) Accidental dural puncture; (2) failure of neuraxial anesthesia requiring conversion to alternative anesthetic techniques; (3) participant withdrawal or loss to follow-up; (4) occurrence of severe complications requiring intensive care unit (ICU) admission.

Randomization and Allocation Concealment

Randomization was conducted based on a computer-generated random number table. Allocation concealment was guaranteed using sequentially numbered, opaque, sealed envelopes prepared by an independent research assistant who took no part in patient recruitment or outcome evaluation. Each envelope was opened only after irreversible group assignment of the corresponding participant, keeping allocation information blinded until subject enrollment was finalized. This trial adopted a double-blinded design: anesthesiologists, surgeons, ward nurses, postoperative follow-up researchers and statistical analysts remained unaware of group allocation throughout the entire study period.

Neuraxial anesthesia and analgesia protocol

Neuraxial anesthesia and analgesia protocol
All parturients fasted for 6–8 hours and abstained from oral fluids for 2 hours preoperatively. Upon entering the operating room, electrocardiographic monitoring was initiated using a monitoring equipment (CARESCAPE Monitor B560, GE Healthcare,USA) to measure non-invasive blood pressure, pulse oxygen saturation (SpO2), heart rate (HR), electrocardiogram (ECG). An 18-G intravenous cannula was inserted for venous access, connected to a fluid warmer. Preload was achieved with hydroxyethyl starch infused at 10–15 mL/(kg·h), and active temperature management was implemented with a forced-air warming blanket.

The parturient was placed in the left lateral position. After routine skin disinfection and draping, combined spinal-epidural anesthesia (CSEA) was performed. Local infiltration anesthesia was administered with 5 mL of 1% lidocaine at the L2–L3 intervertebral space. An 16-G epidural needle was advanced until loss of resistance upon penetration of the ligamentum flavum. A 25-G pencil-point spinal needle was then inserted intrathecally. Following aspiration of clear cerebrospinal fluid, 2.2 mL of 0.75% ropivacaine hydrochloride was injected. The spinal needle was withdrawn, and an epidural catheter was advanced 3 cm cephalad through the epidural needle. The epidural needle was removed, and the catheter secured properly.

The patient was turned supine with the operating table tilted 15°to the left. Cold saline was used to assess the sensory block level, which was maintained between T4 and T8. Infusion rate was titrated according to blood pressure and heart rate. Intermittent intravenous boluses of 4 μg norepinephrine were administered for hypotension, while 0.5 mg intravenous atropine was given for bradycardia to maintain mean arterial pressure (MAP) and heart rate (HR) within ± 20% of baseline values.

All patients received 3 mg intravenous tropisetron prior to the end of surgery, followed by connection to a patient-controlled intravenous analgesia (PCIA) pump (CBI + PCA, Tuoren, China). The analgesic regimen consisted of tramadol 10 mg/kg plus tropisetron 7 mg, diluted with normal saline to a total volume of 100 mL. The pump setting was a background infusion rate of 2 mL/h, bolus dose of 2 mL, and lockout interval of 15 min.

Study Intervention

All parturients received 5 mL of the allocated study drug slowly via the epidural route before skin closure. Group C (Control group): 5 mL normal saline; Group T (Esketamine group): esketamine 0.2 mg/kg diluted to a total volume of 5 mL.

Measurements

The primary outcome of this study was the postoperative resting pain intensity. Secondary outcome measures included multiple dimensional indicators covering dynamic pain, uterine contraction pain, analgesia consumption, perioperative inflammatory stress response, postpartum depressive symptoms, and adverse events.

The postoperative resting pain was assessed using the Numerical Rating Scale (NRS) at 2, 6, 12, 24, and 48 hours after cesarean section. Dynamic pain NRS scores and uterine contraction pain NRS scores were evaluated at 24 hours and 48 hours postoperatively, and the cumulative number of patient-controlled intravenous analgesia (PCIA) bolus requests was simultaneously recorded.

On the day before surgery and on the first day after surgery, 4 mL of venous blood was drawn from the parturient and placed into a sterile tube and stand for 15 minutes, then centrifuged at 4000 rpm for 5 minutes. The serum was extracted and stored in a -80°C biobank for subsequent analysis. The serum levels of cortisol, C-reactive protein (CRP), and interleukin-6 (IL-6) were measured by a professional biotechnology company (ADICON CLINICAL LABORATORIES,LTD., Hangzhou,China) using the ELISA method.

Postpartum depressive symptoms and the incidence of postpartum depression were evaluated using the Edinburgh Postnatal Depression Scale (EPDS), with assessments performed at one day preoperatively, one week postpartum, and six weeks postpartum. The EPDS is a 10-item self-rating scale with total scores ranging from 0 to 30. Higher total scores indicate more severe depressive symptoms, and a score of ≥ 13 was defined as a positive screening result for postpartum depression[9, 16].

In addition, all adverse reactions throughout the observation period were documented, including common postoperative adverse events (postoperative nausea and vomiting, pruritus, and shivering) and psychiatric adverse reactions (dizziness, somnolence, agitation and emotional excitement).

Statistical analyses

Sample size calculation was performed based on the primary outcome indicator, the postoperative resting NRS pain score. Based on our preliminary experimental results, the mean difference in postoperative resting NRS scores between the esketamine group and the control group was 1.2, with a standard deviation of 1.8. A two-tailed test was adopted with a significance level (α) of 0.05 and a

statistical power (1 − β) of 0.80. Using PASS 15.0 software (NCSS, LLC, Kaysville, Utah, USA). The required sample size was 40 participants per group. To compensate for potential participant withdrawal, a 10% dropout rate was incorporated into the estimation. Accordingly, the initial enrollment size was determined as 44 patients for each group.

All statistical analyses were performed using SPSS 26.0 statistical software (IBM Corp., Armonk, New York, USA). Continuous data were tested for normal distribution using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean ± standard deviation (± SD), and independent-samples t-test was used for inter-group comparison, while repeated-measures analysis of variance (ANOVA) was applied for comparison of repeated measurement indicators at different time points within and between groups. Non-normally distributed continuous variables were expressed as median and interquartile range, and analyzed using the Mann–Whitney U test. Categorical data, were presented as numbers and percentages, and compared using the Chi-square test or Fisher's exact test as appropriate. All statistical tests were two-tailed, and a *P* value < 0.05 was considered statistically significant.

Results

After screening, a total of 88 parturients were recruited, of which four refused to participate in the trial. 84 parturients were randomly assigned to either the control group or the esketamine group. Two parturients in each group were converted to general anesthesia due to inadequate neuraxial anesthesia effects. No parturients were lost to follow-up. Ultimately, 40 parturients from the control group or the esketamine group, completed the statistical analysis(Fig. 1).The baseline and demographic characteristics were comparable between the two groups(Table 1).

Table 1 Baseline and demographic characteristics

	Control group (n=40)	**Esketamine group (n=40)**	t/x^2	***P Value***
Age (years）	28.4±3.7	29.4±3.7	-1.27	0.207
Gestational age (weeks)	38.3±0.9	38.5±1.1	-0.47	0.641
BMI（kg/m2）	28.0±3.0	28.2±2.8	-0.25	0.803
Operative time (min)	55±10.2	54±8.4	0.38	0.702
ASA			0.06	0.805
Ⅱ	11(27.5%)	12(30.0%)		
Ⅰ	29(72.5%)	28(70.0%)		

The data are represented as the mean ± SD or number (percentage). ASA, American Society of Anesthesiologists; BMI,Body mass index; n, number; SD, standard deviation; Continuous data were compared by Student's t-test; categorical data were compared using the chi-square(χ2) test.

Repeated-measures ANOVA demonstrated significant main effects of group and time on postoperative resting NRS scores (group effect: $F = 26.66$, $P < 0.001$; time effect: $F = 23.99$, $P < 0.001$), while no significant interaction effect was observed ($F = 0.53$, $P = 0.712$). Compared with Group C, Group T exhibited significantly lower resting NRS scores at 2 h-48 h postoperatively (all $P < 0.05$, Fig. 2). For dynamic pain and uterine contraction pain, Group T obtained markedly lower NRS scores than Group C at both 24 h and 48 h postoperatively (all $P < 0.05$). In addition, the number of PCIA bolus requests within 48 hours after surgery was significantly reduced in Group T compared with Group C ($P < 0.05$, Table 2).

Table 2
Postoperative NRS pain scores at different time points

Rest NRS score	**time point**	**Control group (n = 40)**	**Esketamine group (n = 40)**	***t***	***P Value***
	2h post-op	**4.1 ± 1.3**	**3.5 ± 1.3**	**2.04**	**0.044[a]**
	6h post-op	**4.1 ± 1.3**	**3.1 ± 1.2**	**3.40**	**0.001[a]**
	12h post-op	**3.8 ± 1.3**	**3.0 ± 1.2**	**2.59**	**0.012[a]**
	24h post-op	**3.0 ± 1.3**	**2.5 ± 1.1**	**2.02**	**0.038[a]**
	48h post-op	**2.5 ± 1.0**	**2.0 ± 1.2**	**2.07**	**0.042[a]**
Dynamic NRS score	24h post-op	4.2 ± 1.1	3.6 ± 1.1	2.46	0.016[a]
	48h post-op	3.6 ± 1.2	3.0 ± 1.2	2.15	0.035[a]
Uterine contraction pain NRS score	24h post-op	3.7 ± 1.2	3.1 ± 1.1	2.36	0.021[a]
	48h post-op	3.3 ± 1.3	2.7 ± 1.2	2.19	0.031[a]
Number of rescue analgesia requests	48h post-op	2.7 ± 1.4	1.9 ± 1.4	2.56	0.012[a]

The data are represented as the mean ± SD ; NRS, Numerical Rating Scale. Compared with the control group, [a]$P<0.05$; Mixed-design repeated-measures analysis of variance (ANOVA) was adopted for repeated measurement data. Independent-samples t-test was applied for intergroup comparisons. ANOVA of resting NRS scores: main effect of group, $F = 26.66$, $P < 0.001$; main effect of time, $F = 23.99$, $P < 0.001$; interaction effect, $F = 0.53$, $P = 0.712$.

Preoperative serum cortisol, CRP, and IL-6 levels were similar between the two groups, with no statistically significant differences (all $P > 0.05$). At 24 hours after cesarean section, serum stress and inflammatory biomarkers in both groups were significantly increased compared with preoperative levels. However, Group T showed significantly lower postoperative 24 h levels of cortisol, CRP, and IL-6 than Group C (all $P < 0.05$, Table 3).

Table 3
Perioperative inflammatory indicators in parturients

		Control group (n = 40)	Esketamine group (n = 40)	*t*	*P Value*
Cortisol (nmol/L)	Preoperative Day	291.6 ± 57.3	269.7 ± 62.7	1.63	0.108
	Postoperative Day 1	443.0 ± 89.5	397.6 ± 84.1	2.34	0.022[a]
CRP(mg/L)	Preoperative Day	7.9 ± 3.0	8.3 ± 2.9	-0.58	0.567
	Postoperative Day 1	39.2 ± 13.1	32.0 ± 11.6	2.62	0.011[a]
IL-6(pg/mL)	Preoperative Day	9.3 ± 2.5	10.7 ± 3.9	-1.87	0.066
	Postoperative Day 1	51.1 ± 20.4	40.5 ± 15.9	2.58	0.012[a]

The data are represented as the mean ± SD; CRP, C-reactive protein; IL-6, Interleukin-6. Compared with the control group, [a]$P<0.05$; The data were compared by Student's t-test.

Baseline preoperative EPDS scores were comparable between the two groups ($P > 0.05$). Repeated-measures ANOVA revealed significant group and time main effects on EPDS scores (group effect: $F = 7.99$, $P = 0.006$; time effect: $F = 22.68$, $P < 0.001$), whereas no significant interaction was detected ($F = 1.13$, $P = 0.325$). At 1 week and 6 weeks postpartum, Group T had significantly lower EPDS scores than Group C (all $P < 0.05$). Consistent with the scale scores, the incidence of postpartum depression in Group T was significantly lower than that in Group C at 1 week (7.5% vs. 25.0%, $P = 0.034$) and 6 weeks postpartum (5.0% vs. 20.0%, $P = 0.043$, Table 4).

Table 4
EPDS scores and incidence of postpartum depression

		Control group (n = 40)	Esketamine group (n = 40)	t/χ^2	*P Value*
EPDS scores	Preoperative Day	3.8 ± 1.8	3.4 ± 1.8	0.94	0.353
	1 week post-op	6.5 ± 2.8	5.3 ± 2.7	2.08	0.041[a]
	6 weeks post-op	5.6 ± 2.3	4.3 ± 2.8	2.31	0.024[a]
Incidence of PPD	1 week post-op	10(25.0%)	3(7.5%)	4.50	0.034[a]
	6 weeks post-op	8(20.0%)	2(5.0%)	4.11	0.043[a]

The data are represented as the mean ± SD or number (percentage); EPDS, Edinburgh Postnatal Depression Scale; PPD, Postpartum depression. Compared with the control group, [a]$P<0.05$; Mixed-design repeated-measures analysis of variance (ANOVA) was adopted for repeated measurement EPDS scores. Independent-samples t-test was applied for intergroup comparisons at each time point. ANOVA of EPDS scores: main effect of group, $F = 7.99$, $P = 0.006$; main effect of time, $F = 22.68$, $P < 0.001$; interaction effect, $F = 1.13$, $P = 0.325$. categorical data were compared using the chi-square (χ2) test.

The incidences of commom adverse reaction were similar between Group C and Group T (all $P > 0.05$). Moreover, the incidence of psychiatric adverse reactions was slightly higher in Group T than in Group C; however, the difference was not statistically significant (all $P > 0.05$, Table 5).

Table 5
Incidence of Postoperative Adverse Reactions

Nausea and vomiting	**Control group (n = 40)**	**Esketamine group (n = 40)**	***χ²***	***P Value***
	8(20.0%)	**8(20.0%)**	**0.00**	**1.000**
Pruritus	3(7.5%)	4(10.0%)	0.16	0.692
Shivering	5(12.5%)	4(10.0%)	0.13	0.723
Dizziness	2(5.0%)	3(7.5%)	0.21	0.644
Somnolence	1(2.5%)	2(5.0%)	0.35	0.556
Agitation/excitement	0(0.0%)	1(2.5%)	1.01	0.314
Overall incidence of adverse events	16(40.0%)	19(47.5%)	0.46	0.499

The data are represented as a number (percentage); Data were compared using Fisher's exact test.

Discussion

This prospective randomized double-blind controlled trial enrolled parturients receiving elective cesarean delivery under neuraxial anesthesia, and administered a single epidural dose of 0.2 mg/kg esketamine prior to skin closure. We systematically evaluated its impacts on multidimensional postoperative pain, perioperative inflammatory stress, the risk of postpartum depression (PPD), and drug safety. The results demonstrated that epidural esketamine significantly alleviated resting pain, movement-evoked pain and uterine cramping pain after cesarean section, and reduced demands for PCIA. It suppressed the elevation of postoperative inflammatory cytokines and stress hormones, and lowered EPDS scores as well as PPD screening positivity at 1 and 6 weeks postpartum. Although the incidence of mild psychiatric adverse reactions slightly increased in the esketamine group, the between-group difference was statistically insignificant, indicating satisfactory overall safety. The present study supplements clinical evidence supporting epidural esketamine for multimodal perioperative analgesia in obstetrics. Herein, we elaborate on the relevant mechanisms, clinical implications, and limitations of this trial.

Post-cesarean pain consists of incisional resting pain, activity-induced pain and uterine contraction pain. Severe pain activates systemic stress responses, delays early mobilization and lactation recovery, and serves as an independent risk factor for PPD. Consistent with our hypothesis, the esketamine group exhibited markedly lower NRS scores for resting pain from 2 h to 48 h postoperatively, accompanied by reduced movement and uterine pain scores at 24 and 48 h, as well as fewer PCIA bolus requests within 48 h. These findings verify that a single epidural injection of esketamine produces sustained, comprehensive postoperative analgesia.

Esketamine acts as a noncompetitive NMDA receptor antagonist to block spinal dorsal horn NMDA receptors and inhibit central hyperalgesia. Preservative-free esketamine formulations have been validated to be safe and efficacious for epidural administration in several previous studies [17–19]. Surgical traction and incisional trauma during cesarean delivery, together with postpartum uterine involution, continuously stimulate nociceptors and trigger systemic inflammatory cascades, which lower pain thresholds via peripheral nociceptor sensitization[3]. Epidural esketamine effectively blocks nociceptive signaling pathways and exerts robust analgesia against both incisional and uterine pain[20]. Furthermore, it reduces postoperative opioid consumption and mitigates postoperative hyperalgesia[21]. When combined with tramadol-based PCIA, epidural esketamine generates synergistic analgesia, cutting rescue analgesic requirements and lowering the potential risk of opioid-related adverse events. Administered before skin closure, esketamine preemptively inhibits the initiation of postoperative hyperalgesia by intercepting impending persistent nociceptive input after surgical trauma, which explains the significant intergroup difference in pain scores observed as early as 2 h postoperatively. Our data confirm epidural esketamine as a valuable adjuvant analgesic for multimodal pain management after cesarean delivery.

Acute postoperative pain and PPD are two highly prevalent, interrelated perioperative complications, with perioperative inflammation acting as a critical mediator linking the two. Prior studies have reported positive correlations between antenatal serum levels of IL-1β, IL-6, CRP and the severity of postpartum depressive symptoms; each median absolute increase in inflammatory biomarkers elevates the risk of

severe PPD by over 30%[22, 23]. Modulation of perioperative inflammation reshapes the trajectory of postoperative pain [24]. Conversely, painful stimuli further exacerbate inflammatory responses, creating a self-amplifying vicious cycle that substantially raises the risk of postpartum mood disorders and impairs maternal mobility, breastfeeding adherence and long-term physical and mental well-being. Baseline serum cortisol, CRP and IL-6 concentrations were comparable between groups in our cohort, while all inflammatory and stress biomarkers rose markedly 24 h after surgery in both arms. Nevertheless, the magnitude of elevation was significantly attenuated in the esketamine group, demonstrating its capacity to alleviate excessive perioperative inflammatory stress. Mechanistically, esketamine exerts anti-inflammatory effects by modulating monocyte-macrophage function, suppressing core inflammatory signaling pathways, and regulating the secretion of specific cytokines [25–27]. Exaggerated inflammatory stress in cesarean parturients increases susceptibility to postpartum infection, poor wound healing and psychiatric comorbidities. Collectively, epidural esketamine concurrently blocks nociceptive transmission and inflammatory cascades, facilitating holistic physical recovery after delivery.

PPD represents the most common psychological complication following cesarean section, with persistent mood disturbances impairing mother-infant bonding, hindering breastfeeding and imposing long-term psychological burdens on families. Our follow-up data revealed substantially lower EPDS scores and PPD screening rates in the esketamine group at both 1 and 6 weeks postpartum; PPD positivity dropped from 25.0% to 7.5% at 1 week, and from 20.0% to 5.0% at 6 weeks, proving that epidural esketamine alleviates depressive symptoms and reduces PPD risk. As the S-enantiomer of ketamine, esketamine shares identical pharmacological profiles with enhanced potency. Ketamine elicits antidepressant effects via multiple pathways: By blocking various subtypes of NMDAR and suppressing abnormal burst firing in the lateral habenula, ketamine exerts antidepressant effects, while its metabolite (2R,6R)-hydroxynorketamine acts independently of NMDARs. These pathways jointly activate α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptorα(AMPAR), brain-derived neurotrophic factor（BDNF）and mammalian target of rapamycin（mTOR）cascades to restore damaged excitatory synapses, and its anti-inflammatory property further alleviates inflammation-induced depressive symptoms, producing rapid and sustained antidepressant benefits [28]. Our results confirm that the mood-improving effects of epidural esketamine persist long-term, supporting its dual roles in comprehensive analgesia and perinatal emotional regulation as a promising preventive intervention against PPD.

Postoperative nausea and vomiting, pruritus and shivering are common adverse events associated with neuraxial anesthesia combined with opioids, whereas dizziness, drowsiness, irritability, emotional lability and blurred vision are characteristic psychotomimetic side effects of ketamine derivatives. In this trial, the incidence of nausea/vomiting, pruritus and shivering was similar across groups. Although mild psychiatric reactions occurred slightly more frequently in the esketamine group, no statistically significant intergroup difference was detected. All psychiatric manifestations were transient and mild, resolving spontaneously without targeted intervention; no severe adverse events including hallucinations, severe agitation or consciousness disturbance were recorded. These findings validate

that epidural esketamine at 0.2 mg/kg carries no clinically meaningful safety risks and can be safely administered as an adjuvant analgesic for cesarean parturients.

Several limitations of the present study should be acknowledged. First, this was a single-center trial restricted to low-risk women with singleton term pregnancies, so our findings cannot be generalized to high-risk obstetric populations. Second, only a fixed single dose (0.2 mg/kg) of epidural esketamine was adopted without dose gradient comparisons, precluding clarification of dose-effect relationships and optimal therapeutic windows. Third, inflammatory cytokines were only measured at baseline and 24 h postoperatively, lacking serial dynamic data at 48 h and 1 week postpartum to fully characterize temporal inflammatory fluctuations. Fourth, PPD screening solely relied on the EPDS without confirmatory structured psychiatric interviews, introducing potential false-positive and false-negative biases.Future multi-center stratified trials enrolling diverse high-risk obstetric cohorts are warranted to expand the generalizability of these results. Graded esketamine doses should be tested to identify the optimal safe epidural dosage for patients stratified by body weight and pregnancy risk. Additional serial blood sampling at 48 h and 1 week postpartum will delineate complete inflammatory kinetic profiles. Combined EPDS screening and standardized psychiatric diagnostic interviews will improve the accuracy of PPD identification.

Conclusions

Single epidural administration of 0.2 mg/kg esketamine prior to skin closure enhances postoperative pain relief, suppresses perioperative inflammation, and alleviates postpartum depressive symptoms after cesarean section. The incidence of mild psychiatric side effects was slightly higher but not statistically significant. Epidural esketamine appears to be a safe adjuvant analgesic for parturients receiving cesarean delivery.

Abbreviations

AMPARα
amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
ANOVA Analysis of variance

ASA American Society of Anesthesiologists

BMI Body mass index

CSEA Combined spinal-epidural anesthesia

CRP C-reactive protein

ECG Electrocardiogram

ELISA Enzyme-linked immunosorbent assay

EPDS Edinburgh Postnatal Depression Scale

HNK (2R,6R)-hydroxynorketamine

HR Heart rate

ICU Intensive care unit

IL-6 Interleukin-6

MAP Mean arterial pressure

mTOR Mammalian target of rapamycin

NMDA N-methyl-D-aspartic acid

NMDAR N-methyl-D-aspartate receptor

NRS Numerical Rating Scale

PCIA Patient-controlled intravenous analgesia

PONV Postoperative nausea and vomiting

PPD Postpartum depression

SD Standard deviation

SpO_2 Saturation of peripheral oxygen

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ningbo Medical Center Lihuili Hospital,China(KY2024SL110-01) and the protocol was registered at the Chinese Clinical Trial Registry (ChiCTR2400090341) (Retrospectively registered). The initial registration date was 27/09/2024. All procedures performed in this study involving human participants were in accordance with the Ethical Standards of the Institutional Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients signed written informed consent before surgery.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Author Contribution

Tingting Qiu and Hong-lin Fu were involved in study concept and design;Hong-lin Fu collected the data; Yun Yang and Yuefeng Zhou analyzed the data, prepared figures ;Tingting Qiu and Hong-lin Fu drafted the article; Tingting Qiu revised the manuscript.

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Data Availability

The data presented in this study are available on request from the corresponding author due to privacy and ethical restrictions.

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Figures

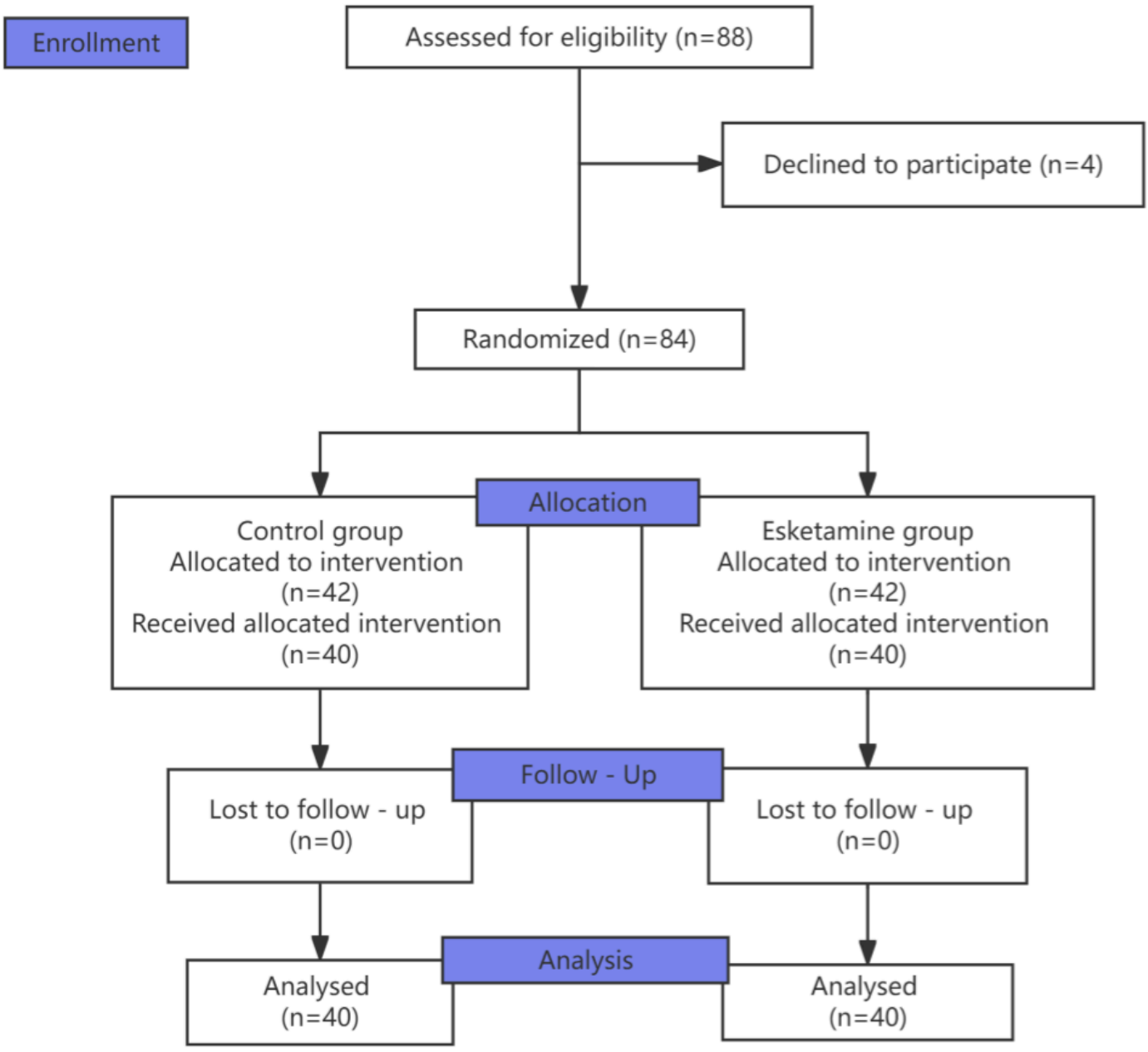


Figure 1

Flow chart of the participants

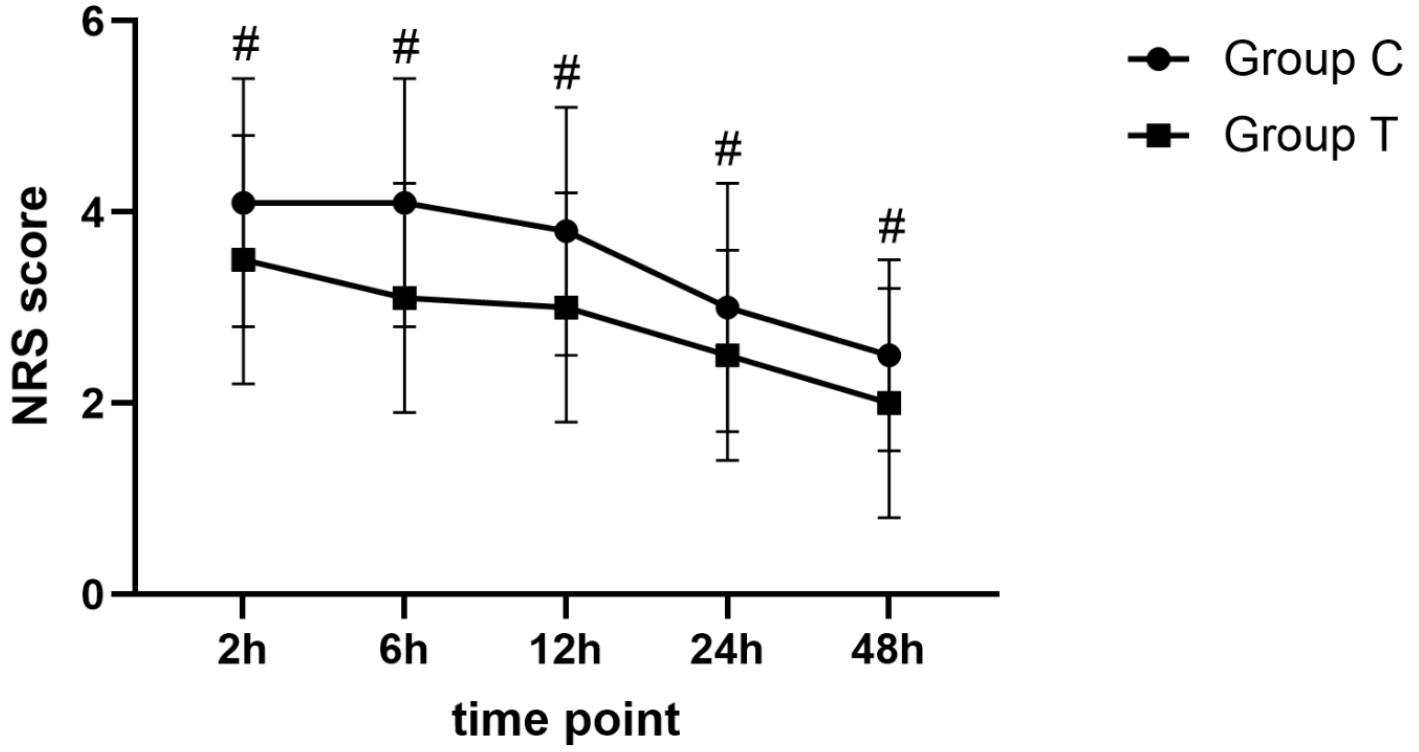


Figure 2

Line chart of NRS score of parturients at different time points. NRS, Numerical Rating Scale. Compared with GroupC, $^{\#}P<0.05$.