RESEARCH ARTICLE

Effects of esketamine on postoperative pain, anxiety, depression, sleep, and inflammation in pregnancies undergoing cesarean section: A randomized controlled trial

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Abstract

Objective

Postoperative pain is the most notable issue after cesarean section (CS). The contributing factors include hyperalgesia, anxiety, depression, sleep disorders, and inflammation. In this study, we explored the effects of esketamine on pain, hyperalgesia, depression, anxiety, sleep disorders, and inflammation after CS.

Methods

This randomized, blinded, controlled trial enrolled single-term pregnant women scheduled for elective CS. This trial was a single-center study conducted at Chongqing University Fuling Hospital. A simple randomization method was used. SPSS version 26.0 generated random numbers. The participants were randomly included in the esketamine group (group E: intravenous esketamine 0.5 mg/kg + sufentanil 4 μg/kg followed by patient-controlled intravenous analgesia with esketamine 0.5 mg/kg) or the control group (C: normal saline + sufentanil 4 μg/kg PCIA). The primary outcome was the maximum pain numerical rating scale (NRS) score within 24 h postoperatively. The secondary outcomes included pain NRS scores for moving incision, visceral, and rest incision pain at 0–6 h, 6–12 h and 12–24 h; pressure pain threshold and tolerance at 30 min and 24 h postoperatively; PCIA drug consumption, number of compressions, and dosage of rescue analgesics; time to first PCIA compression; serum C-reactive protein (CRP) at 24 h; incidence of drug-related side effects; and rates of anxiety, depression, and sleep disorders on postoperative day 2.

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Results

Ninety-eight women were randomly included in group E (n = 50) or C (n = 48). Group E showed significantly lower maximum NRS pain scores within 24 h (5 [4–5] vs. 6 [5–6], $P < 0.0001$) and relieved rest incision, visceral, and moving incision pain at all time points. The PCIA compression was significantly delayed and CRP levels, as well as the incidence of postoperative depression, anxiety, and sleep disorders, were lower in group E. There were no statistically significant differences in hyperalgesia or side effects between the groups.

Conclusion

Intravenous esketamine could effectively reduce postoperative pain, psychological disorders, and inflammation after CS.

This study was registered in the Chinese Clinical Trial Registry with registration number ChiCTR2300078310.

Introduction

Pain is the most notable issue following cesarean section (CS) [1]. The incidence of acute moderate-to-severe postoperative pain after CS is as high as 68% [2]; chronic pain occurs from 15.2% to 25.5% of cases [3,4]. Pain significantly affects postoperative recovery, mental state, breastfeeding, and the mother-infant relationship. Patient-controlled intravenous analgesia (PCIA) is a commonly used analgesic method in clinical practice. However, high-dose opioids are associated with side effects such as constipation, nausea and vomiting, and respiratory depression; they may also lead to tolerance, addiction, and hyperalgesia [5]. Therefore, there is an urgent need for exploring new multimodal postoperative analgesic methods to relieve postoperative pain following CS.

Inflammatory reactions caused by tissue injury not only lead to inflammatory pain but also activate nerve terminals to generate action potentials that are transmitted to N-methyl-D-aspartic acid (NMDA) receptors in the spinal cord through the dorsal root ganglia. These signals activate specific brain areas to decrease the pain threshold, resulting in hyperalgesia [6,7]. Moreover, pain has a bidirectional relationship with postoperative depression, anxiety, and sleep disorders [8]. Therefore, inflammation, hyperalgesia, anxiety, depression, and sleep disorders are important factors for aggravating pain after CS.

Esketamine is a novel analgesic with a non-competitive antagonistic effect on NMDA receptors, which may alleviate hyperalgesia. It also exhibits anti-inflammatory properties and has been shown to improve postpartum depression and sleep disorders [9–13]. However, studies on its use in pregnancies undergoing CS are limited. Therefore, in this study, we explored the effect of esketamine on postoperative pain after CS, including its impact on inflammation, hyperalgesia, anxiety, depression, and sleep disorders.

Methods

This randomized, blind, placebo-controlled trial was approved by the Chongqing University Fuling Hospital ethics committee (2023CDFSFLYYEC-064) and registered in the Chinese Clinical Trial Registry (registration number: ChiCTR2300078310). This study was conducted in Chongqing university Fuling Hospital. All procedures were performed in accordance with the Declaration of Helsinki guidelines (2024 edition) and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines (2025 edition) (Fig 1). All participants were informed about the trial details and provided written informed consent.

Inclusion criteria

The inclusion criteria were women aged 20–45 years, with singleton full-term pregnancies, who underwent elective CS under combined spinal-epidural anesthesia, had American Society of Anesthesiologists (ASA) Physical Status Class II–III, and voluntarily participated after providing signed informed consent.

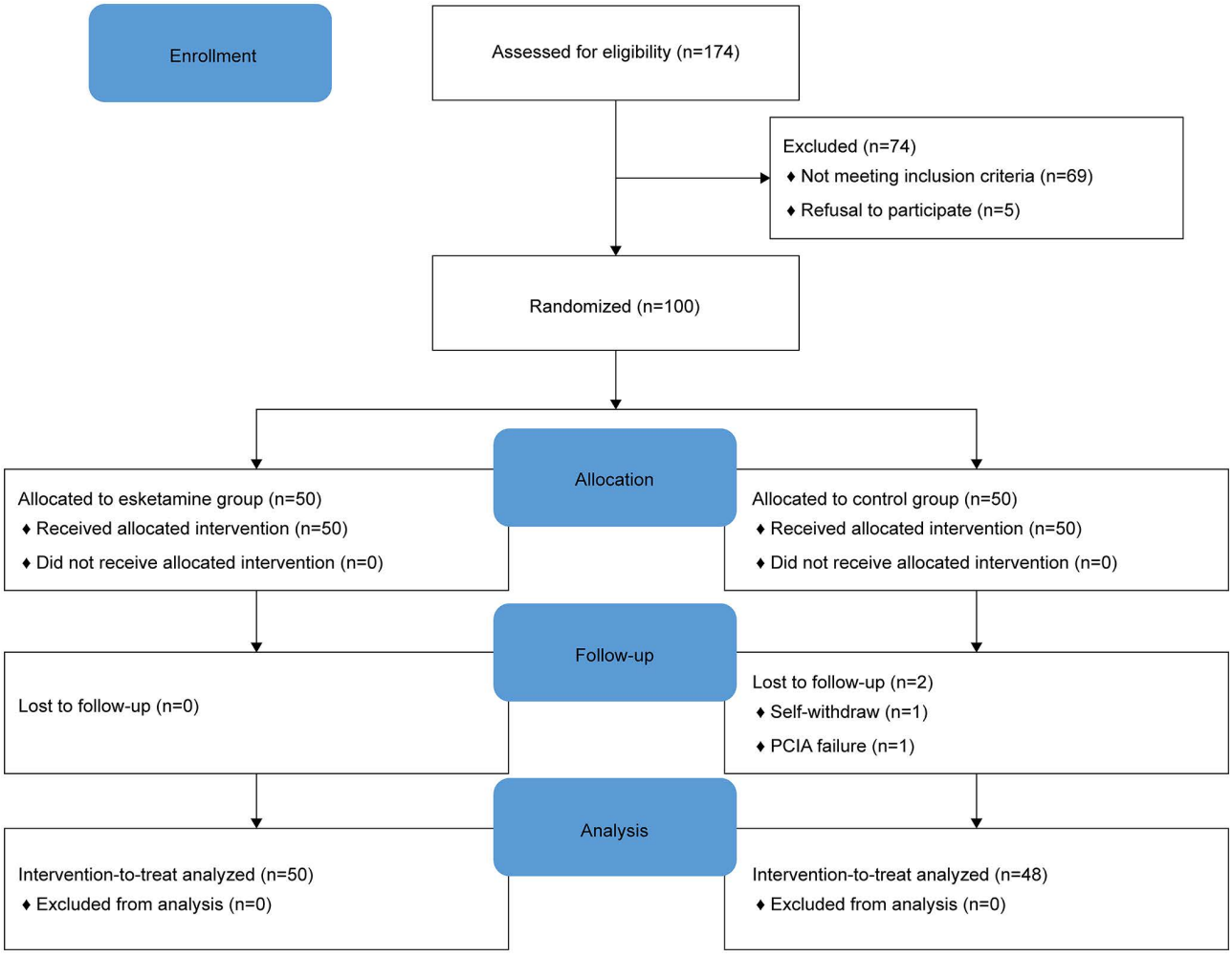

Fig 1. CONSORT flowchart of the study.

https://doi.org/10.1371/journal.pone.0328585.g001

Exclusion criteria

We excluded pregnancies with contraindications to CS, such as intrauterine stillbirth, fetal malformation, maternal intolerance to surgery, and fetal distress; contraindications to combined spinal-epidural anesthesia, such as coagulation dysfunction and central nervous system disorders; contraindications to any study drugs, including esketamine and sufentanil; history of alcoholism or chronic opioid, hormone, or anti-inflammatory/analgesic drug use; allergy to the study drugs; or inability or unwillingness to cooperate or provide informed consent.

Randomization and masking

A simple randomization method was used. Random numbers were generated in a 1:1 ratio by an independent researcher using SPSS version 26.0 (IBM Corp, Armonk, NY). A researcher, who was not involved in the study or data analysis, assigned the sequence and placed the random numbers in light-tight, sealed numbered envelopes. The participants were consecutively enrolled and randomly included in the esketamine group (group E) or control group (group C). Before anesthesia, another researcher not involved in the data collection and analysis prepared the study drugs (colorless and transparent, 20 ml in total) and PCIA (all were colorless and transparent, totaling 200 ml) according to the random number allocation. All drugs and PCIA were labeled only as "investigational drugs" to mask their identity. The envelopes were re-secured after completion of the intervention. The anesthesiologists, participants, data analysts, and outcome assessors were all blinded to group assignments.

Preoperative data collection

Informed consent was obtained 1 day before the CS. Demographic data and comorbidities were recorded. The Pittsburgh Sleep Quality Index was used for assessing the sleep status in the previous month. The Athens Insomnia Scale was used for evaluating postoperative sleep quality on day 2. The Edinburgh Postnatal Depression Scale and Generalized Anxiety Disorder scale were used for respectively evaluating depression and anxiety preoperatively and on postoperative day 2.

A digital algometer pain diagnostic gauge (WAGNER, FDIX25 WAGNER INTERNATIONAL AG, USA [unit: kgf]) was used for testing the pressure pain threshold (PPT) and pressure pain tolerance (PTO). The algometer was applied vertically to the skin at each test point; pressure was applied slowly and uniformly. PPT was defined as the pressure at which pain was first perceived; moreover, PTO was the pressure at which pain became intolerable (Fig 1). Three test points, spaced 2 cm apart, were marked on the dominant forearm. The average values of the three measurements were recorded (Fig 2).

Anesthesia and surgery method

After admission to the operating room, the participants were continuously monitored for vital signs including electrocardiography, pulse oxygen saturation, non-invasive blood pressure, and respiratory rate. A peripheral venous channel input was opened using Ringer's solution at 500 ml/h. Combined spinal-epidural anesthesia was performed using a median puncture approach at the L3–4 spinal segment. In the subarachnoid space, 1.5 ml of 1% ropivacaine + 1.5 ml of 10% glucose injection, totaling 3 ml, was administered. A 4 cm epidural catheter was then inserted cephalad. Norepinephrine was administered via infusion to maintain the mean arterial pressure at ≥80% or ≥60 mmHg. If the heart rate dropped below 50 bpm, 0.3 mg of atropine was intravenously administered. If oxygen saturation was < 90% or there was respiratory depression, 60% oxygen was administered via a mask. The CS was performed using a Pfannenstiel incision with peritoneal closure. After clamping the umbilical cord, oxytocin (10 IU) was intravenously infused. At the end of the operation, intravenous palonosetron (0.25 mg; Hengrui Pharmaceutical Co., LTD., Jiangsu, China) was provided to prevent postoperative nausea and vomiting.

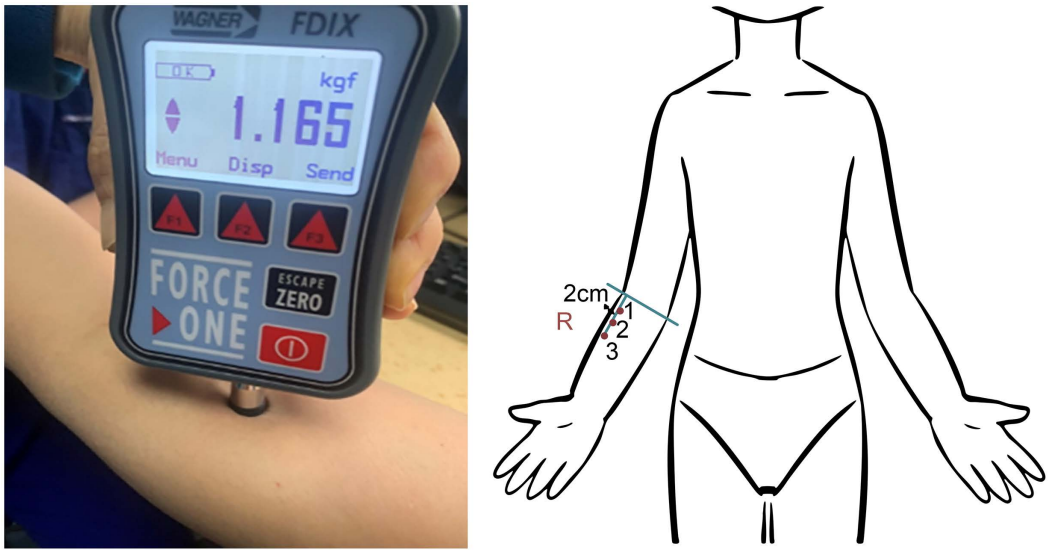

Fig 2. Pressure pain threshold and pressure pain tolerance measurements. A: Digital algometer pain diagnostic gauge; B: Test points at the dominant forearm.

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Intervention

In group E, immediately after umbilical cord clamping, esketamine (0.5 mg/kg; Hengrui Pharmaceutical Co., LTD., Jiangsu, China) was slowly injected intravenously for approximately 1 min. A PCIA pump containing sufentanil (4 μg/kg; Yichang Renfu Pharmaceutical Co., LTD., Hubei, China), 0.5 mg/kg of esketamine, and 0.25 mg of palonosetron, diluted with normal saline to 200 ml, was connected at the end of the surgery.

In Group C, immediately after umbilical cord clamping, intravenous injection of the same amount of normal saline was administered. The PCIA pump contained 4 μg/kg of sufentanil and 0.25 mg of palonosetron, also diluted with normal saline to 200 ml.

The PCIA parameter settings included: initial dose, 0 ml; constant infusion dose, 2 ml/h; bolus dose, 3 ml/time; locking time, 15 min; and maximum dose per h, 14 ml. If the PCIA dose reached the maximum and the patient reported significant pain (numeric rating scale [NRS] score ≥4), 50 mg of tramadol was injected intravenously.

Outcomes

The primary outcome was the maximum NRS pain score within 24 h postoperatively. The secondary outcomes were the pain NRS scores for moving incision, visceral, and rest incision pain at 0–6 h, 6–12 h, and 12–24 h; time of the first PCIA compression, number of compressions (NOC), dosage of rescue analgesics, and total PCIA drug consumption during each time interval; PPT and PTO at 30 minutes and 24 hours postoperatively; serum C-reactive protein (CRP) concentration and incidence of drug-related side effects at 24 hours postoperatively; and incidence of anxiety, depression, and sleep disorders on postoperative day 2.

Sample size calculation

This was a prospective trial. Based on data from our preliminary study, the expected maximum pain score at 24 h after CS was 6.5 ± 0.9 in the control group and 4.0 ± 1.0 after prophylactic esketamine administration. Based on difference test, we calculated that 45 participants would be needed in each group according to the 1:1 parallel control difference test, using

SPSS sample size calculation software, test level of 2.5%, and test efficiency of 90%. Considering 10% loss to follow-up, the final sample size was set at 50 participants per group, for a total of 100 participants.

Statistical analysis

Continuous variables that conformed to the normal distribution are expressed as mean ± standard deviation ($\bar{x} \pm s$), while those with a non-normal distribution are expressed as median (interquartile range [IQR]) [M (Q25, Q75)]. Categorical variables are expressed as absolute values and frequencies. Data conforming to a normal distribution were compared using independent sample t-tests. Non-normally distributed variables (e.g., NRS pain scores) were analyzed using non-parametric tests (Mann–Whitney U tests). Fisher's exact probability method or chi-squared tests were used to compare differences in nausea and vomiting, dizziness, drowsiness, nightmares, and diplopia between the groups. SPSS version 26.0 was used for all statistical analyses. $P \leq 0.05$ was set as the threshold of statistical significance.

Results

We screened 174 pregnant women, of whom, 100 were included and randomly assigned to the esketamine group (n = 50) or control group (n = 50). The first and final participants were included on December 12, 2023 and April 18, 2025 respectively. There was no unblinding throughout the study period. In group C, two participants dropped out: 1 withdrew owing to PCIA failure 3 h postoperatively and 1 voluntarily withdrew 8 h after surgery. The remaining 98 participants completed the study procedure and data analysis.

At baseline, the age of the participants was significantly lower in group E than in group C; group C included more cases of gestational hypothyroidism. There were no significant differences in terms of gestational age, demographic characteristics (weight, height, and body mass index), history of CS, or other complications (Table 1).

The maximum NRS pain score within 24 h after surgery was lower in group E than in group C (median [IQR]: 5 [4–5] vs. 6 [5–6], $P < 0.0001$). In addition, the maximum NRS scores for moving incision, visceral, and rest incision pain were significantly lower in group E than in group C at any period (Fig 3).

Rest incision pain:

- 0–6 h: 1 [0–1.25] vs. 1 [1–2], $P < 0.0001$
- 6–12 h: 1 [1–2] vs. 2 [1.25–2], $P < 0.0001$
- 12–24 h: 2 [1–2] vs. 2 [1, 3], $P < 0.0001$

Table 1. Demographic characteristics of the participants in the two groups.

	Group E	Group C
Age (years)	29.86 ± 3.38	31.63 ± 4.74
Height (cm)	159.78 ± 4.71	158.48 ± 5.30
Weight (kg)	73.33 ± 9.28	72.56 ± 9.25
Body mass index (kg/m^2)	28.70 ± 3.26	28.90 ± 3.58
Gestation age (weeks)	38.74 ± 0.88	38.62 ± 0.89
Hypothyroidism, n (%)	6 (12%)	15 (31.2%)
Gestational diabetes mellitus, n (%)	12 (24%)	12 (25%)
Prior history of CS, n (%)	21 (42%)	21 (43.8%)
Oligohydramnios, n (%)	9 (18%)	8 (16.7%)

Data are presented as number (proportion) or mean (SD). CS: Cesarean section

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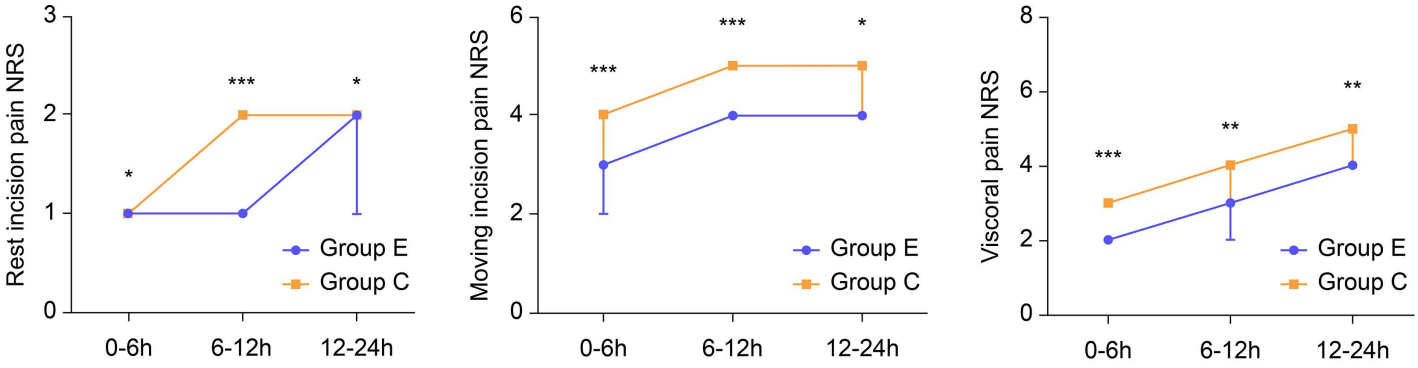

Fig 3. Comparison of NRS scores for rest incision, moving incision, and visceral pain between Group E and Group C at each postoperative time point. NRS: Numeric Rating Scale.

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Moving incision pain:

- 0–6 h: 3 [2–3] vs. 4 [3–4], $P < 0.0001$
- 6–12 h: 4 [34–5] vs. 5 [4–5], $P < 0.0001$
- 12–24 h: 4 [4–5] vs. 5 [4–5], $P = 0.016$

Visceral pain:

- 0–6 h: 2 [2–3] vs. 3 [3–4], $P < 0.0001$
- 6–12 h: 3 (2–4) vs. 4 [34–5], $P = 0.003$
- 12–24 h: 4 [2.75–4.25] vs. 5 [4–5. 75], $P < 0.0001$.

Group E also showed significantly lower cumulative resting, moving, and visceral pain NRS scores than did group C (Table 2).

The time to first PCIA compression was significantly delayed in group E compared with that in group C. However, there were no differences between the groups in NOC and total PCIA consumption at any time point (Table 3). One pregnancy in group C received 150 mg of tramadol as rescue analgesia.

The preoperative and postoperative PPT and PTO values showed no significant difference between the groups.

PPT (kgf):

- T0: 2.1 [1.62–2.4] vs. 2.2 [1.59–2.86], $P = 0.677$
- T1: 2.18 [1.76–2.6] vs. 2.33 [1.79–2.95], $P = 0.440$
- T2 2.03 [1.6–2.83] vs. 2.15 [1.8–2.8], $P = 0.376$)

Table2. Comparison of cumulative pain NRS scores.

	Group E (n = 50)	Group C (n = 48)	P Value
Cumulative resting pain score	4 (3–5)	5(4–6)	$P < 0.0001$
Cumulative moving pain score	11 (10–12)	13 (12–14.75)	$P < 0.0001$
Cumulative visceral pain score	9.14 ± 3.02	11.79 ± 2.47	$P < 0.0001$

Data are presented as inter-quartile range or mean (SD).

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Table 3. Usage of the PCIA pump.

	Group E (n = 50)	Group C (n = 48)	P Value
Time of first PCIA compression (min)	159.00 (94.75–261.25)	91.00 (41.50–154.00)	$P < 0.0001^{*}$
0–6 h postoperatively NOC of PCIA (times)	3.00 (1.75–5.00)	2.00 (1.25–5.00)	0.724
6–12 h postoperatively NOC of PCIA (times)	2.50 (1.00–4.00)	2.00 (0.00–3.75)	0.229
12–24 h postoperatively NOC of PCIA (times)	4.00 (2.00–7.25)	3.00 (2.00–6.75)	0.358
0–6 h postoperatively PCIA consumption (mL)	18.00 (15.75–24.00)	18.00 (15.00–24.75)	0.679
6–12 h postoperatively PCIA consumption (mL)	18.00 (15.00–24.00)	16.50 (12.00–24.00)	0.427
12–24 h postoperatively PCIA consumption (mL)	34.00 (30.00–43.50)	33.00 (27.00–44.25)	0.625

Data are presented as interquartile ranges.

PCIA: patient-controlled intravenous analgesia, NOC: number of compressions.

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PTO (kgf):

- T0: 4 [3.2–5.05] vs. 4.25 [3.36–5.2], $P = 0.513$
- T1: 4.29 [3.1–5.3] vs. 4.4 [3.38–5.56], $P = 0.558$
- T2: 3.88 [2.62–4.83] vs. 3.85 [3.33–4.92], $P = 0.272$ (Fig 4)

The preoperative sleep, anxiety, and depression evaluations were not significantly different between the groups. However, on postoperative day 2, the incidence of sleep disorders, postpartum depression, and anxiety was significantly lower in group E (Table 4).

There was no difference in preoperative serum CRP concentrations (3.70 ± 1.40 vs. 4.08 ± 1.78 mg/L, $P = 0.237$). However, the postoperative serum CRP concentration was significantly higher in group C than in group E (73.92 ± 28.20 vs. 59.32 ± 17.24 mg/L, $P = 0.003$) (Fig 5).

Using the multivariate regression analysis, we found that age had no effect on the primary outcome, whereas hypothyroidism was positively correlated (Fig 6).

The incidence of side effects (dizziness, nausea and vomiting, drowsiness, nightmares, and diplopia) was not significantly different between the groups (Table 5).

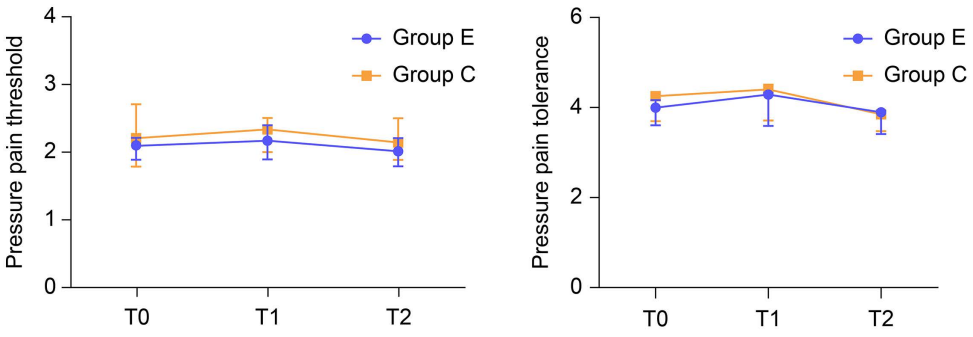

Fig 4. Comparison of preoperative and postoperative PPT and PTO between the groups. PPT: pressure pain threshold, PTO: pressure pain tolerance.

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Table 4. Comparison of anxiety, depression, and sleep disorders between the groups.

	Group E (n = 50)	Group C (n = 48)	P Value
Preoperative sleep quality			
Good	42 (84%)	39 (81.3%)	0.567
Relatively good	8 (16%)	4 (8.3%)	
Average	0 (0%)	5 (10.4%)	
Poor	0 (0%)	0 (0%)	
Postoperative sleep quality			
Suspected insomnia	0 (0%)	11 (22.9%)	$P < 0.0001^{*}$
Insomnia	1 (2%)	8 (16.7%)	
No insomnia	49 (98%)	29 (60.4%)	
Preoperative anxiety			
No	43 (86%)	37 (77.1%)	0.228
Mild	7 (14%)	9 (18.8%)	
Moderate	0 (0%)	1 (2.1%)	
Severe	0 (0%)	1 (2.1%)	
Postoperative anxiety			
No	49 (98%)	39 (81.3%)	0.006 *
Mild	1 (1%)	9 (18.7%)	
Moderate	0 (0%)	0 (0%)	
Severe	0 (0%)	0 (0%)	
Preoperative depression			
No	37 (74%)	37 (77.1%)	0.868
Mild	13 (26%)	8 (16.7%)	
Depression	0 (0%)	3(6.2%)	
Postoperative depression			
No	48 (96%)	40 (83.3%)	0.038 *
Mild	2 (4%)	7 (14.6%)	
Depression	0 (0%)	1 (2.1%)	

Data are presented as numbers (proportion).

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Discussion

In this clinical trial, our findings revealed that the combined application of esketamine could effectively alleviate postoperative pain within 24 h after CS and showed an anti-inflammatory effect; it also reduced the incidence of anxiety and depression and improved sleep quality on postoperative day 2. However, esketamine had no significant effect on hyperalgesia.

There are close bidirectional interactions between sleep disorders, anxiety, depression, and pain. Sleep disorders are known to exacerbate pain by disrupting the inflammatory system, aggravating inflammatory responses, and interfering with pain regulation and processing. However, they also heighten pain perception and reduce pain tolerance [14]. Additionally, pain and sleep disorders can significantly increase the risk of anxiety and depression and even lead to suicide [15].

As an optical isomer of ketamine, esketamine blocks pain signal conduction through non-competitive antagonism of NMDA receptors to produce analgesic effects. It also regulates the glutamatergic system, which crucially influences pain, anxiety, depression, and sleep, thereby improving postoperative anxiety, depression, and sleep quality [16]. Our findings of postoperative analgesia and antidepressant effects of esketamine are consistent with those in previous research [17–20]. As far as we know, this is the first study to report the effects of esketamine on anxiety and sleep disorders after CS.

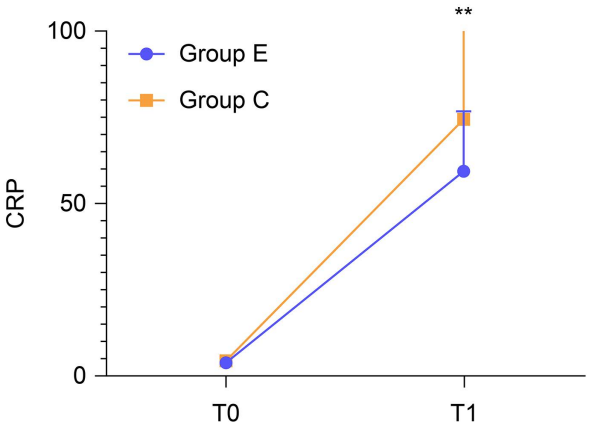

Fig 5. Comparison of serum CRP concentrations between the groups. CRP: C-reactive protein.

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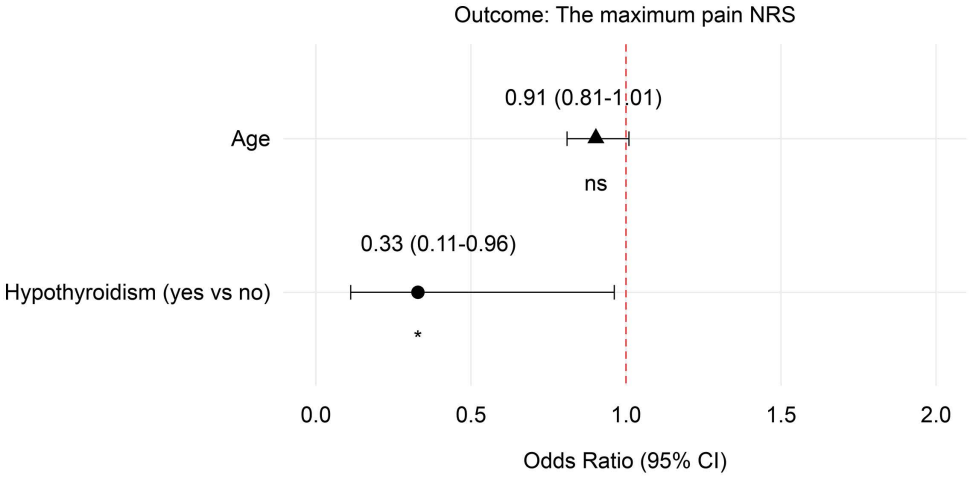

Fig 6. Multivariate regression analysis related to the maximum pain NRS. NRS: numerical rating scale.

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Table 5. Comparison of the incidence of drug-related side effects between the groups.

	Group E (n = 50)	Group C (n = 48)	P Value
Nausea and vomiting	8 (16%)	2 (4.2%)	0.092
Dizziness	4 (8%)	3 (6.3%)	1.000
Drowsiness	5 (10%)	2 (4.2%)	0.436
Nightmare	5 (10%)	2 (4.2%)	0.436
Diplopia	1 (2%)	0 (0%)	1.000

Data are presented as numbers (proportion)

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Tissue injury during surgery induces an inflammatory response that contributes to postoperative pain [21]. This process involves the activation of NMDA receptors in the dorsal horn of the spinal cord through the dorsal root ganglia, leading to neuroinflammation and activating sensory neurons. The result is a lowered pain threshold and increased pain sensitivity, causing hyperalgesia [22]. Therefore, we hypothesized that esketamine may be effective in alleviating post-CS

hyperalgesia owing to its non-competitive NMDA receptor antagonistic effect. Although Ren et al. found that esketamine effectively relieved hyperalgesia after thyroidectomy [23], we found no significant effect on hyperalgesia in our study; we and other research teams have previously reported this finding [24,25]. Hyperalgesia after thyroidectomy may result not only from surgical tissue injury but also from opioid-induced hyperalgesia. Therefore, we hypothesized that esketamine would be more effective in relieving opioid-induced hyperalgesia than that caused by tissue injury.

At baseline, the incidence of pregnant women with preoperative hypothyroidism was significantly higher in group C than in group E. Although reports on the interaction between hypothyroidism and pain are few. Ørstavik et al. suggested that hypothyroidism, which is one of the causes of painful neuropathy, can affect large- and small-fiber function, thereby changing the body's pain sensitivity [26]. Yi et al. in a study on drug-induced hypothyroidism in mice found that hypothyroidism could reduce the thermal pain threshold through mechanisms such as up-regulating the GluR1 subunit, NR2B-containing NMDA receptors, and γ-aminobutyric acid (GABA) A receptors in the anterior cingulate cortex. This promoted glutamatergic synaptic transmission and decreased GABAergic receptor transmission, whereas the mechanical pain threshold did not substantially change [27]. The finding of mechanical pain threshold was consistent with the results of the hyperalgesia test in this study. Therefore, in this study, the higher NRS pain scores observed in group C might reflect the confounding effect of more patients with hypothyroidism.

In addition, the mean age of the participants in group E was lower than that in group C. Wang and Worly discovered in a retrospective study that older pregnant women (aged 36–45 years) had a higher demand for analgesic drugs than did younger pregnant women, whereas younger pregnant women exhibited a greater incidence of severe pain [28]. Similarly, Lokeshwar et al. suggested that younger maternal age is associated with more severe postoperative pain, possibly due to anxiety [29]. In our study, despite the younger average age in group E, their NRS pain scores were lower than those in group C, indicating a powerful analgesic effect of esketamine.

There are some limitations of this study. First, this was a single-center study, which might limit the generalizability of the findings across different regions and populations. Second, given concerns about participant recruitment owing to the declining birth rate in China, we set the dropout rate at 10% during the sample size calculation, the overall sample size was relatively small, future multicenter studies with larger sample sizes are required. Third, hypothyroidism was a confounding factor in this study, which might increase the significance of the comparison of pain scores between the two groups and amplify the analgesic effect of esketamine. Fourth, we only detected changes in PPT and PTO on the forearms of the pregnant patients to explore the effect of esketamine on central sensitization. Therefore, further testing its effect on cold and thermal pain on the forearm and peripheral sensitization is necessary to explore its effect on hyperalgesia after CS in detail. Finally, this study was limited to the short-term effects of esketamine after CS. The long-term effects of esketamine on postoperative chronic pain, anxiety, depression, and sleep conditions remain unknown.

Conclusion

Esketamine effectively relieved postoperative pain after CS, reduced anxiety and depression, improved sleep quality, and exerted anti-inflammatory effects. However, it did not affect postoperative hyperalgesia.

Supporting information

S1 Text. Individual participant data.
(XLSX)

S1 File. CONSORT checklist.
(DOC)

S2 File. Trail protocol.
(DOCX)

Author contributions

Investigation: Xiaoliang Zhang.

Methodology: Yijun Wang, Xiang Zou.

Project administration: Junhua Zhang.

Resources: Juanxia Xing.

Software: Li Zhang, Jie Shen.

Validation: Renqin Zhang.

Writing – original draft: Xiaolu Lin.

Writing – review & editing: Daju Zhou.

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