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CLINICAL TRIAL REPORT

Effects of Intraoperative Esketamine–Dexmedetomidine Combination on Postpartum Depressive Symptoms and Neuropsychiatric Events Following Cesarean Delivery: A Randomized Controlled Trial

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Purpose: This trial aims to compare the effects of intraoperative low-dose dexmedetomidine combined with esketamine versus esketamine alone on postpartum depressive and esketamine-related neuropsychiatric adverse events in cesarean delivery.

Patients and Methods: In this randomized controlled trial, 134 parturients scheduled for cesarean delivery under combined spinal-epidural anesthesia were enrolled. Following umbilical cord clamping, patients were randomly allocated to receive either 0.25 mg/kg esketamine combined with 0.5 μg/kg dexmedetomidine (Group DE, n=67) or 0.25 mg/kg esketamine alone (Group E, n=67). The study assessed Edinburgh Postnatal Depression Scale (EPDS) scores on postpartum days 7 and 42, the incidence of esketamine-related neuropsychiatric adverse events, maternal satisfaction, postoperative pain scores, and other adverse events.

Results: On postpartum day 7, the Group DE exhibited significantly lower EPDS scores than the Group E (median [IQR]: 3.00 [2.00–4.00] vs 4.00 [3.00–5.00]; $P < 0.001$). This between-group difference was no longer significant at the 42-day follow-up. The overall incidence of neuropsychiatric adverse events was significantly reduced in the Group DE [22 (32.84%) vs 39 (58.21%), $P = 0.003$], with notably fewer cases of dizziness (19.40% vs 35.82%, $P = 0.034$) and headache (8.96% vs 23.88%, $P = 0.020$). Additionally, the Group DE had lower rates of nausea (8.96% vs 23.88%, $P = 0.020$) and tachycardia (20.90% vs 47.76%, $P = 0.001$), and higher maternal satisfaction scores [10.00 (9.00–10.00) vs 9.00 (9.00–10.00), $P = 0.005$].

Conclusion: Combined low-dose dexmedetomidine and esketamine during cesarean section provides a short-term improvement in early postpartum depressive symptoms, reduces intraoperative neuropsychiatric adverse events, and enhances maternal satisfaction, with a favorable maternal and neonatal safety profile.

Keywords: dexmedetomidine, esketamine, cesarean section, postpartum depressive, neuropsychiatric adverse events, maternal satisfaction

Introduction

Postpartum depression (PPD) is the most common perinatal mental health condition, affecting an estimated 15–30% of women globally, with a prevalence in China of approximately 25%.[1–3] Symptoms of postpartum depression most commonly begin to manifest within the first week after delivery, and approximately half of cases may persist for more than a year, significantly impairing maternal well-being and recovery.[4,5] Disruptions in mother-infant bonding associated with PPD can adversely affect infant behavioral, emotional, and cognitive development. In severe cases, PPD may lead to

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suicidal ideation or behavior.[6–9] As such, PPD constitutes a major global public health issue, underscoring the urgent need for early prevention and effective intervention.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has shown rapid antidepressant effects in major depressive disorder and treatment-resistant depression.[10,11] Its S-enantiomer, esketamine, exhibits approximately twofold greater affinity for the NMDA receptor and was approved by the US Food and Drug Administration in 2019 for treatment-resistant depression.[12] Recent studies indicate that perioperative intravenous esketamine during cesarean delivery significantly reduces early postpartum depressive symptoms and lowers the incidence of major depressive episodes at 42 days postpartum.[13,14] Meta-analyses confirm that both ketamine and esketamine are effective in preventing postpartum depression, with esketamine demonstrating superior efficacy.[15,16] However, its use is limited by sympathomimetic effects (eg, hypertension, tachycardia) and a high incidence of neuropsychiatric adverse events (eg, dissociation, dizziness), which may impair treatment adherence.[14,17] Combination strategies may help optimize its therapeutic potential.

Dexmedetomidine, a highly selective α_2-adrenergic receptor agonist, provides sedation, analgesia, amnesia, and anxiolysis without respiratory depression, making it valuable in obstetric anesthesia.[18] A meta-analysis of 13 studies indicated that early postpartum dexmedetomidine administration significantly lowers postpartum depression symptom scores.[19] While preliminary evidence supports its potential for alleviating postpartum depression, further multicenter randomized controlled trials are required to confirm its efficacy. However, dexmedetomidine can inhibit sympathetic activity via spinal preganglionic neurons, potentially causing hypotension and bradycardia.[20] Notably, esketamine has been shown to reduce intraoperative hypotension in anxious parturients during cesarean delivery.[21] Recent work by Yang et al demonstrated that combining esketamine (0.3 mg/kg) with dexmedetomidine (0.5 μg/kg) safely improves visceral traction pain relief and hemodynamic stability compared to dexmedetomidine alone.[22]

As a pilot exploratory study, this trial aims to compare whether adding low-dose dexmedetomidine to esketamine improves the risk-benefit profile for cesarean delivery by evaluating differences in antidepressant effects, perioperative comfort, and neuropsychiatric adverse events between the two interventions.

Methods

Ethics and Study Design

This double-blind, randomized controlled trial was conducted at the First Affiliated Hospital of Anhui Medical University. The study protocol received approval from the hospital's Ethics Committee (Approval No. PJ2024-08-72) and was registered with the Chinese Clinical Trial Registry (Registration No. ChiCTR2400088820) prior to participant enrollment. The trial adhered to the CONSORT guidelines and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Participants

This study enrolled pregnant women aged 18–45 years with full-term singleton pregnancies scheduled for elective cesarean delivery under combined spinal-epidural anesthesia. Exclusion criteria comprised: (1) pre-pregnancy body mass index (BMI) >27 kg/m^2; (2) history of mental disorders, central nervous system diseases, or severe hepatic, renal, cardiopulmonary dysfunction, or American Society of Anesthesiologists (ASA) physical status >III; (3) severe obstetric complications including preeclampsia, eclampsia, gestational hypertension, placenta previa, or placental abruption; (4) intrauterine fetal demise or congenital anomalies; (5) contraindications to neuraxial anesthesia such as coagulopathy, anticoagulant use, hemodynamic instability, or shock; (6) inability to comply with study procedures due to sensory or cognitive impairment; (7) known hypersensitivity or contraindication to the study drugs; or (8) bradycardia (heart rate <50 bpm), cardiac conduction abnormalities, or preoperative hypotension (systolic blood pressure <90 mmHg).

Participants were withdrawn if any of the following occurred: conversion to general anesthesia, a serious adverse event, obstetric or fetal complications requiring protocol deviation, or voluntary withdrawal. All case report forms for withdrawn participants were retained and analyzed in accordance with both intention-to-treat and per-protocol principles.

Randomization and Blinding

The random allocation sequence was generated by an independent statistician using block randomization (block size of 4) in R software (version 4.4.1). Participants were randomly allocated in a 1:1 ratio to receive either 0.25 mg/kg esketamine combined with 0.5 μg/kg dexmedetomidine (Group DE) or 0.25 mg/kg esketamine (Group E). The allocation sequence was concealed using sequentially numbered, opaque, sealed envelopes.

Prior to anesthesia induction, an independent research coordinator prepared the study drugs according to the envelope assignment. For Group DE, Drug A consisted of 0.5 μg/kg dexmedetomidine diluted to 20 mL with normal saline, and Drug B contained 0.25 mg/kg esketamine in 10 mL. For Group E, Drug A was 20 mL normal saline (placebo), and Drug B was identical in formulation to that of Group DE. All solutions were visually indistinguishable and labeled only with participant ID and drug code (A or B). The prepared syringes were delivered directly to the attending anesthesiologist. All participants, clinical staff, and outcome assessors remained blinded throughout the study.

Sample Size Calculation

The sample size was calculated for the two co-primary outcomes using PASS 15.0 software, with a two-sided α of 0.05, 90% power, and a 20% allowance for dropouts.

Based on Edinburgh Postnatal Depression Scale (EPDS) Score

Preliminary data (means: 4.9 vs 3.1; σ=2.8) indicated a requirement of 52 participants per group. This was adjusted to 65 per group (Total: 130).

Based on Neuropsychiatric Adverse Events

The sample size was calculated based on preliminary data, which showed a 60% incidence of neuropsychiatric adverse events in the esketamine monotherapy group. To detect a clinically meaningful 50% relative reduction in incidence (from 60% to 30%) with combination therapy, a minimum of 67 participants per group was required. Accordingly, a total of 134 participants were planned for enrollment.

The larger sample size of 134 participants was selected to ensure adequate power for both primary outcomes. All participants were randomized in a 1:1 ratio to Group E (0.25 mg/kg esketamine) or Group DE (0.25 mg/kg esketamine combined with 0.5 μg/kg dexmedetomidine).

Implementation Methods

No preoperative medications were administered, and all parturients remained fasting as per routine. Upon arrival in the operating room, standard monitoring was applied, including heart rate (HR), blood pressure (BP), and oxygen saturation (SpO_2), and peripheral intravenous access was established.

Combined spinal-epidural anesthesia was performed with the patient in the left lateral decubitus position. Using an AS-E needle, the L2-L3 or L3-L4 interspace was punctured. The epidural space was identified by loss-of-resistance with air or saline. A S-shaped spinal needle was then advanced into the subarachnoid space; after confirming free flow of cerebrospinal fluid, 12–15 mg of 0.5% ropivacaine (2.4–3.0 mL) was injected. The spinal needle was withdrawn, and an epidural catheter was inserted 3–4 cm cephalad. The parturient was turned supine with left uterine displacement and given oxygen at 5 L/min via face mask. A test dose of 3 mL of 2% lidocaine was administered through the epidural catheter. After a 5-minute observation period, sensory block level was assessed using an alcohol swab. A T4–T6 sensory block was maintained by titrating additional 0.5% ropivacaine containing 1% lidocaine as needed. Following umbilical cord clamping, Drug A was administered as a 10-minute intravenous infusion, immediately followed by an intravenous bolus of Drug B. If a bilateral T6 sensory block was not achieved within 20 minutes after initiating the epidural supplementation regimen (5-mL boluses of 0.5% ropivacaine with 1% lidocaine at 5-minute intervals, up to 15 mL total), the combined spinal-epidural anesthesia was deemed unsuccessful and converted to general anesthesia.

All patients received a preload of 10 mL/kg crystalloid solution rapidly over 15–20 minutes before induction of anesthesia. Apgar scores were assessed at 1 and 5 minutes after delivery. Intraoperative systolic blood pressure was maintained within 20% of baseline or ≥90 mmHg; decreases below this threshold were treated with intravenous

norepinephrine (4–12 μg). Bradycardia (HR <50 bpm) was managed with intravenous atropine (0.3–0.5 mg). Postoperative analgesia was maintained for 48 hours using patient-controlled epidural analgesia with a solution containing 200 mg ropivacaine and 100 μg sufentanil in 100 mL normal saline, administered as a continuous infusion at 2 mL/h.

Data Collection and Outcome Assessment

Baseline data comprised demographic characteristics, obstetric history (including gestational age and pregnancy-related comorbidities), BMI, and preoperative EPDS scores. Intraoperative data included surgical and anesthesia duration, fluid infusion volume, estimated blood loss, use of vasoactive agents, and vital signs (HR, BP, SpO_2) recorded immediately after delivery (t_0) and at 5-minute intervals for 40 minutes (t_1-t_8). Postoperative data collected included pain scores, time to first flatus and lactation initiation, breastfeeding method, maternal satisfaction (assessed by Visual Analog Scale, VAS), total hospital stay, and the incidence of adverse events. Postoperative pain was evaluated with the Numerical Rating Scale (NRS, 0–10), with rescue analgesia administered for NRS scores >4.

The study employed dual co-primary outcomes to comprehensively assess the intervention: (1) the EPDS score, assessed in a structured interviewer-administered format on postpartum day 7 (within 24 hours of that day); and (2) the incidence of intraoperative neuropsychiatric adverse events, incidence of neuropsychiatric adverse events, including dizziness, headache, agitation (Richmond Agitation-Sedation Scale ≥2), hallucination, blurred vision, diplopia, nystagmus, and daymare. A statistically significant result favoring the intervention group on either co-primary outcome constituted trial success. The EPDS is scored from 0 to 30, with higher scores indicating more severe depressive symptoms. A score of 10 or higher is typically used to define a positive screen.[23,24]

Secondary outcomes included: (1) EPDS score on postpartum day 42; (2) maternal satisfaction assessed by VAS at the end of surgery; (3) incidence of other adverse events such as nausea and vomiting, shiver, hypertension (systolic BP >160 mmHg or >30% increase from baseline), hypotension (systolic BP <90 mmHg or >30% decrease), tachycardia (HR >100 bpm), bradycardia (HR <50 bpm), respiratory depression (respiratory rate <10 breaths/min), and hypoxemia (SpO_2 <90%); and (4) postoperative pain intensity, frequency of rescue analgesia, breastfeeding method, time to first flatus and lactation initiation, and total hospital stay.

Statistical Analysis

Statistical analyses were performed using R studio 4.4.1 (R studio, Boston, MA, USA). Continuous variables were tested for normality with the Kolmogorov–Smirnov test. Normally distributed data are described as mean ± standard deviation (SD) and compared between groups using the independent samples *t*-test; repeated-measures analysis of variance (ANOVA) was used for longitudinal comparisons. Non-normally distributed data are summarized as median (interquartile range [IQR]) and analyzed with the Mann–Whitney *U*-test (between groups) or the Friedman test (over time). Categorical variables are presented as numbers (percentages) and compared with the chi-square test or Fisher's exact test, as appropriate. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient Enrollment and Baseline Characteristics

Between October 20, 2024 and August 20, 2025, 178 parturients were assessed for eligibility; 134 were enrolled and randomized (Figure 1). Baseline characteristics were well-balanced between the two groups (Table 1).

The Group DE had a significantly lower need for epidural supplementation than the Group E [6 (8.96%) vs 15 (22.39%), P = 0.032]. No significant differences were observed between groups in time to T6 sensory block, surgical duration, time to delivery, anesthetic dosage, intraoperative fluid volume, estimated blood loss, neonatal birth weight, Apgar scores at 1 and 5 minutes, or neonatal destination (Table 2).

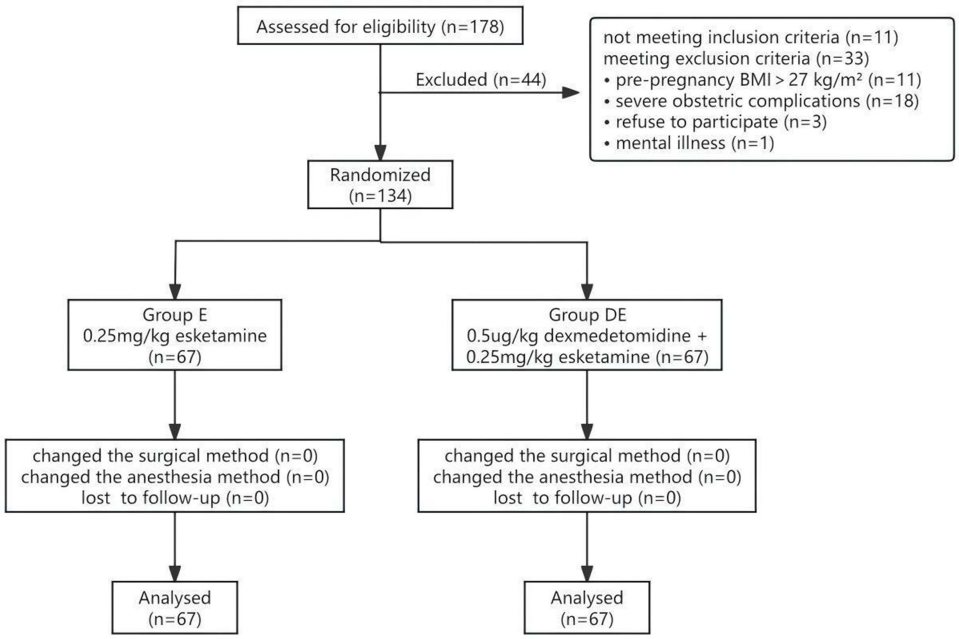

Figure 1 Flow chart of patient enrollment.

Primary Outcomes

On postpartum day 7, the median EPDS score was significantly lower in Group DE (3.00 [IQR 2.00–4.00]) than in Group E (4.00 [IQR 3.00–5.00]; P < 0.001). This difference was not sustained at postpartum day 42 (5.00 [2.00–6.00] vs 6.00 [5.00–7.00]; P = 0.075) (Table 3).

The incidence of intraoperative neuropsychiatric adverse events, a co-primary outcome, was also significantly lower in Group DE than in Group E (32.84% vs 58.21%, P = 0.003). Specifically, Group DE had reduced rates of dizziness (19.40% vs 35.82%, P = 0.034) and headache (8.96% vs 23.88%, P = 0.020). The frequencies of other neuropsychiatric adverse events (including agitation, sedation, drowsiness, hallucinations, blurred vision, diplopia, nystagmus, and nightmares) were comparable between groups (Table 3).

Table 1 Demographic and Baseline Data in Patients

Variables	Group DE (n = 67)	Group E (n = 67)	*P* value
Age (years)	32.90 ± 3.69	32.19 ± 3.64	0.270
Height (cm)	160.00 (158.00, 164.00)	160.00 (158.00, 164.50)	0.795
Pre-pregnancy weight (kg)	56.87 ± 6.81	57.43 ± 7.52	0.665
Pre-pregnancy BMI (kg/m^2)	22.30 ± 2.89	22.11 ± 2.37	0.982
Weight at delivery (kg)	68.78 ± 6.97	70.60 ± 7.89	0.161
BMI at delivery (kg/m^2)	27.00 (25.45, 28.50)	27.30 (25.25, 29.40)	0.212
ASA physical status			0.282
2	56 (83.58)	51 (76.12)	
3	11 (16.42)	16 (23.88)	
Duration of education (years)			0.315
<9	1 (1.49)	1 (1.49)	
9-12	19 (28.36)	12 (17.91)	
>12	47 (70.15)	54 (80.60)	
Marital status			1.000
Unmarried	0 (0.00)	1 (1.49)	
Married	67 (100)	66 (98.51)	

(*Continued*)

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Table 1 (Continued).

Variables	Group DE (n = 67)	Group E (n = 67)	*P* value
Full time employment	48 (71.64)	43 (64.18)	0.355
Covered by social health insurance	57 (85.07)	57 (85.07)	1.000
Stressful life events within 2 years	4 (5.97)	6 (8.96)	0.511
Smoking	0 (0)	0 (0)	>0.999
Alcohol intake	0 (0)	0 (0)	>0.999
Prepartum haemoglobin (g/L)	120.27 ± 10.02	119.33 ± 10.98	0.606
Preoperative EPDS score	6.00 (4.00, 8.00)	6.00 (5.00, 8.00)	0.105
Insomnia Severity Index	3.00 (2.00, 5.00)	4.00 (3.00, 6.00)	0.181
Number of pregnancies			0.649
1	16 (23.88)	23 (34.33)	
2	22 (32.84)	18 (26.87)	
3	14 (20.90)	13 (19.40)	
4	7 (10.45)	7 (10.45)	
5	4 (5.97)	4 (5.97)	
6	4 (5.97)	1 (1.49)	
7	0 (0.00)	1 (1.49)	
Number of deliveries			0.127
0	23 (34.33)	35 (52.24)	
1	33 (49.25)	23 (34.33)	
2	10 (14.93)	9 (13.43)	
3	1 (1.49)	0 (0.00)	
Planned pregnancy			0.685
Yes	50 (74.63)	52 (77.61)	
No	17 (25.37)	15 (22.39)	
Gestational age (days)	270.52 ± 6.53	271.46 ± 6.27	0.397
Pregnancy complications			
Gestational diabetes	24 (35.82)	30 (44.78)	0.291
Hypothyroidism	11 (16.42)	6 (8.96)	0.194
Anemia	1 (1.49)	3 (4.48)	0.612
Paternal data			
Smoking	27 (40.30)	32 (47.76)	0.384
Alcohol intake	15 (22.39)	25 (37.31)	0.059
Education >12 years	51 (76.12)	56 (83.58)	0.275
Full time employment	67 (100)	67 (100)	>0.999

Notes: Values are presented as mean ± SD, median (interquartile range), or number (percentage). P <0.05 indicates statistically significant difference.

Abbreviations: BMI, Body Mass Index; ASA, American Society of Anesthesiologists; EPDS, Edinburgh postnatal depression scale.

Secondary Outcomes and Safety Endpoints

For secondary outcomes, Group DE showed significantly lower rates of nausea (8.96% vs 23.88%; P = 0.020) and tachycardia (20.90% vs 47.76%; P = 0.001), along with higher maternal satisfaction scores (median 10.00 [IQR 9.00–10.00] vs 9.00 [9.00–10.00]; P = 0.005) compared to Group E (Table 4). No significant differences were observed between groups in other adverse events, postoperative pain scores, rescue analgesia use, breastfeeding outcomes, or recovery parameters. No severe adverse events were reported postoperatively in either group.

Changes in mean arterial pressure (MAP) and HR over the 40 minutes following drug administration are shown in Figure 2. At t_2 (10 minutes), MAP was significantly higher in Group DE (89.70 mmHg) than in Group E (84.35 mmHg), with no significant differences at other time points. From t_2 to t_8, HR remained consistently higher in Group E compared to Group DE (P < 0.05). The incidence of PPD at 7 days postpartum was 11.94% (8/67) in Group E, 7.46% (5/67) in Group DE (7.46% vs 11.94%, P =0.381), and the between-group difference was not statistically significant (Table S1).

Table 2 Intraoperative Data and Neonatal Outcomes

Variables	Group DE (n = 67)	Group E (n = 67)	*P* value
Time for block plane to T6 (min)	10.00 (10.00, 15.00)	11.00 (10.00, 15.00)	0.477
Surgical duration (min)	55.00 (48.50, 64.00)	54.00 (46.00, 60.50)	0.425
Time of fetal delivery (min)	8.00 (6.00, 10.50)	7.00 (6.00, 10.50)	0.954
Ropivacaine (mg)	13.00 (12.50, 14.00)	14.00 (12.50, 15.00)	0.069
Lidocaine (mg)	40.00 (40.00, 50.00)	40.00 (40.00, 50.00)	0.892
Esketamine (mg)	17.50 (16.25, 18.25)	17.50 (16.25, 18.88)	0.300
Dexmedetomidine (μg)	35.00 (32.50, 36.50)	–	–
Fluid infusion (mL)	1600.00 (1100.00, 1600.00)	1600.00 (1150.00, 1600.00)	0.916
Estimated blood loss (mL)	400.00 (400.00, 400.00)	400.00 (400.00, 400.00)	0.957
Use of vasoactive drugs	21 (31.34)	21 (31.34)	1.000
Use of additional analgesics	6 (8.96)	15 (22.39)	0.032
Use of antiemetics	6 (8.96)	12 (17.91)	0.129
Neonatal data			
Male sex	40 (59.70)	42 (62.69)	0.723
Weight (g)	3250.00 (2980.00, 3515.00)	3270.00 (3055.00, 3510.00)	0.244
Apgar-1min	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	0.655
Apgar-5min	10.00 (10.00, 10.00)	10.00 (10.00, 10.00)	>0.999
Destination (ward)	67 (100)	67 (100)	>0.999

Notes: Values are presented as mean ± SD, median (interquartile range), or number (percentage). P <0.05 indicates statistically significant difference.
Abbreviation: Apgar, range 0–10 with higher scores indicating healthier newborns.

Table 3 EPDS Score and Neuropsychiatric Adverse Events

Variables	Group DE (n = 67)	Group E (n = 67)	*P* value
EPDS score at 7 days	3.00 (2.00, 4.00)	4.00 (3.00, 5.00)	<0.001
EPDS score at 42 days	5.00 (5.00, 6.00)	6.00 (5.00, 7.00)	0.075
Neuropsychiatric adverse events	22 (32.84)	39 (58.21)	0.003
Dizziness	13 (19.40)	24 (35.82)	0.034
Headache	6 (8.96)	16 (23.88)	0.020
Agitation	0 (0.00)	4 (5.97)	0.128
Sedation	4 (5.97)	1 (1.49)	0.362
Somnolence	5 (7.46)	10 (14.93)	0.171
Hallucination	5 (7.46)	10 (14.93)	0.171
Blurred vision	3 (4.48)	5 (7.46)	0.715
Diplopia	1 (1.49)	1 (1.49)	>0.999
Nystagmus	0 (0.00)	5 (7.46)	0.068
Daymare	0 (0.00)	1 (1.49)	>0.999

Notes: Classification variables are expressed as the patient number (%). Continuous variables are expressed as the median (IQR). P<0.05 indicates a difference among the two groups.
Abbreviations: EPDS, Edinburgh postnatal depression scale, range 0–30 with higher scores indicating more severe depression.

Discussion

In this randomized clinical trial, the addition of low-dose dexmedetomidine to esketamine immediately after umbilical cord clamping, compared to esketamine alone, led to a short-term reduction in early postpartum depressive symptom scores and a lower incidence of neuropsychiatric adverse events, along with higher maternal satisfaction. However, this reduction in symptoms was not sustained at 42 days postpartum and did not significantly decrease the incidence of postpartum depression.

Esketamine (0.25–0.5 mg/kg) is established for reducing PPD risk after cesarean delivery,[25,26] with the 0.25 mg/kg dose offering comparable efficacy and superior safety.[27] Given its established efficacy alongside a more favorable safety

Table 4 Other Adverse Events and Postoperative Data

Variables	Group DE (n = 67)	Group E (n = 67)	*P* value
Other adverse events			
Nausea	6 (8.96)	16 (23.88)	0.020
Vomiting	3 (4.48)	8 (11.94)	0.116
Shiver	0 (0.00)	1 (1.49)	>0.999
Hypertension	0 (0.00)	1 (1.49)	>0.999
Hypotension	5 (7.46)	3 (4.48)	0.715
Tachycardia	14 (20.90)	32 (47.76)	0.001
Bradycardia	0(0.00)	0(0.00)	–
Respiratory depression	0(0.00)	0(0.00)	–
Hypoxemia	0(0.00)	0(0.00)	–
POD1 NRS	2.00 (2.00, 2.00)	2.00 (2.00, 3.50)	0.318
POD2 NRS	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.915
POD3 NRS	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.114
Additional postoperative analgesia	13 (19.40)	16 (23.88)	0.529
Breast feeding	57 (85.07)	59 (88.06)	0.612
Time to initiation of lactation (h)	27.50 (25.75, 29.00)	28.00 (26.00, 28.00)	0.600
Time to first flatus (h)	26.00 (22.00, 32.00)	25.00 (22.50, 30.00)	0.483
Total hospitalization (days)	5.00 (5.00, 6.00)	5.00 (5.00, 6.00)	0.162
Maternal satisfaction score	10.00 (9.00, 10.00)	9.00 (9.00, 10.00)	0.005

Notes: Classification variables are expressed as the patient number (%). Continuous variables are expressed as the median (IQR). P<0.05 indicates a difference among the two groups. Range 0–10, with 0 representing no pain and 10 representing the worst pain.

Abbreviations: POD1, postoperative day 1; POD2, postoperative day 2, POD3, postoperative day 3; NRS, Numerical Rating Scale.

profile, the 0.25 mg/kg dose was selected for this trial. Dexmedetomidine combined with esketamine produces synergistic sedative-analgesic effects, promoting hemodynamic and respiratory stability while improving sleep.[28–30] Consistent with these synergistic properties, our findings demonstrate that this low-dose combination is safe and feasible, and compared to esketamine alone, it provides a transient reduction in early postpartum depressive symptoms, alongside fewer neuropsychiatric adverse events and higher maternal satisfaction.

This study found that the dexmedetomidine–esketamine combination led to a significant yet transient reduction in postpartum depressive symptoms on day 7, without lowering the incidence of PPD at six weeks. This suggests a distinction between acute symptom alleviation and sustained disease modification. Pharmacologically, esketamine provides rapid antidepressant and analgesic effects,[12,31] while dexmedetomidine contributes anxiolytic and sympatholytic activity.[20] Together, they likely mitigate acute perioperative distress and improve early postpartum comfort, without altering long-term PPD risk. Therefore, although the regimen does not prevent PPD, it offers meaningful short-term emotional support, highlighting its potential as an adjunct for managing acute distress after cesarean delivery.

The observed clinical effects of the dexmedetomidine–esketamine combination may be explained by their complementary pharmacological profiles. Esketamine enhances glutamatergic transmission and promotes synaptic plasticity,[32,33] and emerging evidence suggests that its anti-inflammatory properties (eg, via GSK-3β/NLRP3 and Homer1a–mGluR5 pathways) may also contribute to its neuroprotective and mood-modulating effects.[34,35] Dexmedetomidine contributes anxiolytic, sympatholytic, and anti-inflammatory activity,[36] which may help attenuate perioperative stress. Together, these combined actions plausibly support the regimen's transient reduction in early depressive symptoms and improved tolerability observed in this trial.

Dexmedetomidine co-administration reduced esketamine-related neuropsychiatric adverse events and improved hemodynamic stability, likely through its central and peripheral α_2-adrenoceptor-mediated actions. By attenuating sympathetic overactivity and modulating cortical excitability, dexmedetomidine mitigated neuropsychiatric disturbances associated with esketamine.[37] Hemodynamically, dexmedetomidine counteracted esketamine-induced tachycardia via central sympatholysis, while its peripheral α_2B-mediated vasoconstriction contributed to the maintenance of mean arterial

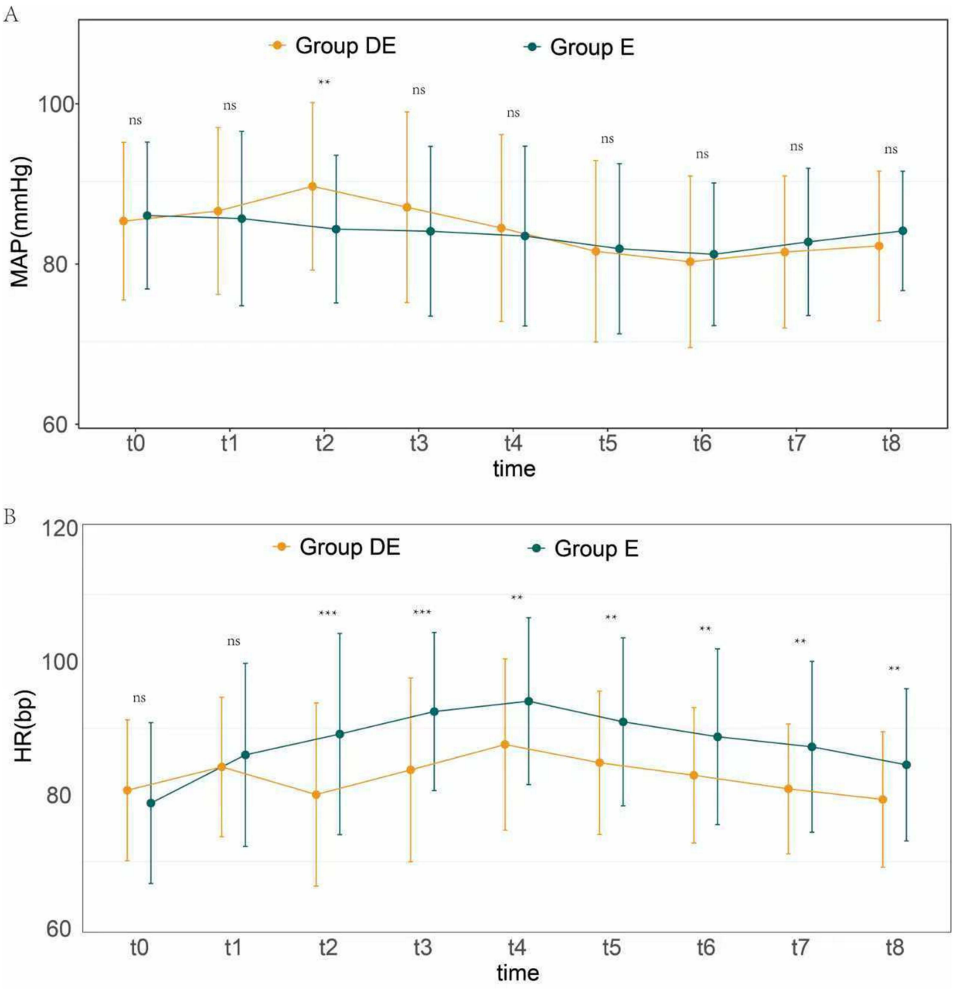

Figure 2 Time-course changes in MAP and HR in both groups: (**A**) MAP over Time; (**B**) HR over Time. ** denotes p<0.01; *** denotes p<0.001; and ns denotes a non-significant difference (p≥0.05).

Abbreviation: MAP, mean arterial pressure; HR, heart rate; t_0: immediately after administration; t_1: 5 minutes post-administration; t_2: 10 minutes post-administration; t_3: 15 minutes post-administration; t_4: 20 minutes post-administration; t_5: 25 minutes post-administration; t_6: 30 minutes post-administration; t_7: 35 minutes post-administration; t_8: 40 minutes post-administration.

pressure, resulting in an overall more stable cardiovascular profile.[17,20,37] Variations in reported adverse event rates across studies may be influenced by differences in dosing and administration protocols.

This study has several limitations. First, its single-center design and predominantly Han Chinese cohort may limit the generalizability of the findings. Second, the absence of a dexmedetomidine-only group precludes direct evaluation of its independent contribution. Third, the results are derived from full-term singleton pregnancies under combined spinal-epidural anesthesia and do not address high-risk subgroups for postpartum depression. Fourth, only a fixed low-dose regimen was evaluated, and the optimal dosing strategy remains to be determined. Although the baseline incidence of anemia was comparable between groups, preoperative iron status (a known risk factor for postpartum depression) was not assessed and may represent a confounding variable.[38,39] Finally, follow-up was limited to 42 days postpartum, leaving the long-term effects on mothers and neonates unclear.

Conclusion

This study found that adding low-dose dexmedetomidine to esketamine provides a combination of short-term benefits and a favorable safety profile, this advantage profile supports its consideration as a useful option for mitigating early postpartum distress and improving perioperative care.

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Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author (Pan-Pan Fang) upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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