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Efficacy of a single low dose of esketamine after childbirth for mothers with symptoms of prenatal depression: randomised clinical trial

Shuo Wang,[1] Chun-Mei Deng,[1] Yuan Zeng,[1] Xin-Zhong Chen,[2] Ai-Yuan Li,[3] Shan-Wu Feng,[4] Li-Li Xu,[2] Liang Chen,[3] Hong-Mei Yuan,[4] Han Hu,[2] Tian Yang,[3] Tao Han,[3] Hui-Ying Zhang,[4] Ming Jiang,[4] Xin-Yu Sun,[5] Hui-Ning Guo,[5] Daniel I Sessler,[6,7] Dong-Xin Wang[1,7]

For numbered affiliations see end of the article

Correspondence to: D-X Wang dxwang65@bjmu.edu.cn (ORCID 0000-0002-3205-1836)

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ABSTRACT

OBJECTIVE

To determine whether a single low dose of esketamine administered after childbirth reduces postpartum depression in mothers with prenatal depression.

DESIGN

Randomised, double blind, placebo controlled trial with two parallel arms.

SETTING

Five tertiary care hospitals in China, 19 June 2020 to 3 August 2022.

PARTICIPANTS

364 mothers aged ≥18 years who had at least mild prenatal depression as indicated by Edinburgh postnatal depression scale scores of ≥10 (range 0-30, with higher scores indicating worse depression) and who were admitted to hospital for delivery.

INTERVENTIONS

Participants were randomly assigned 1:1 to receive either 0.2 mg/kg esketamine or placebo infused intravenously over 40 minutes after childbirth once the umbilical cord had been clamped.

MAIN OUTCOME MEASURES

The primary outcome was prevalence of a major depressive episode at 42 days post partum, diagnosed using the mini-international neuropsychiatric interview. Secondary outcomes included the Edinburgh postnatal depression scale score at seven and 42 days post partum and the 17 item Hamilton depression rating scale score at 42 days post partum (range 0-52, with higher scores indicating worse depression). Adverse events were monitored until 24 hours after childbirth.

RESULTS

A total of 364 mothers (mean age 31.8 (standard deviation 4.1) years) were enrolled and randomised. At 42 days post partum, a major depressive episode was observed in 6.7% (12/180) of participants in the esketamine group compared with 25.4% (46/181) in the placebo group (relative risk 0.26, 95% confidence interval (CI) 0.14 to 0.48; P<0.001). Edinburgh postnatal depression scale scores were lower in the esketamine group at seven days (median difference −3, 95% CI −4 to −2; P<0.001) and 42 days (−3, −4 to −2; P<0.001). Hamilton depression rating scale scores at 42 days post partum were also lower in the esketamine group (−4, −6 to −3; P<0.001). The overall incidence of neuropsychiatric adverse events was higher in the esketamine group (45.1% (82/182) *v* 22.0% (40/182); P<0.001); however, symptoms lasted less than a day and none required drug treatment.

CONCLUSIONS

For mothers with prenatal depression, a single low dose of esketamine after childbirth decreases major depressive episodes at 42 days post partum by about three quarters. Neuropsychiatric symptoms were more frequent but transient and did not require drug intervention.

TRIAL REGISTRATION

ClinicalTrials.gov NCT04414943.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Depression is common among perinatal mothers and has adverse effects on both them and their offspring

Esketamine has a rapid onset antidepressant effect for treatment resistant depression, yet the effect for mothers with perinatal depression is unclear

WHAT THIS STUDY ADDS

Esketamine (0.2 mg/kg) infused immediately after childbirth reduced major depressive episodes at 42 days post partum by about three quarters in mothers with prenatal depression

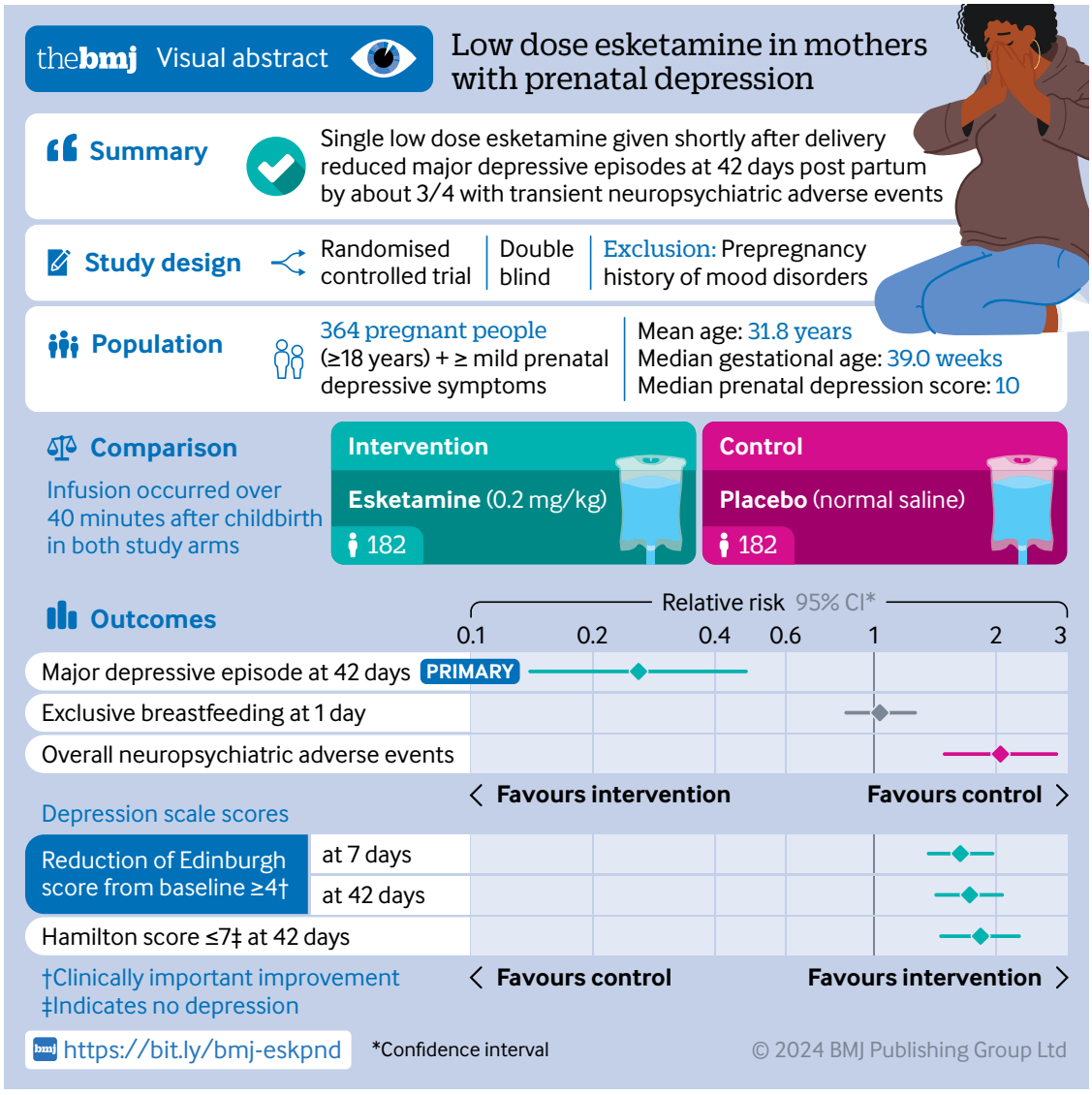
Neuropsychiatric adverse events were more frequent with esketamine, but symptoms lasted less than a day and none required drug treatment

Introduction

Depression is common among women during the perinatal period,[1] with a reported prevalence of 6-13% in high income countries,[2] 21% in middle income countries, and 26% in low income countries.[3] Mothers with perinatal depression are often anxious[4] and have worse relationships with partners[5] and poorer mother-infant attachment than mothers without perinatal depression.[6] The offspring of mothers with depression are at higher risk of behavioural and emotional problems—and even long term psychological and developmental disturbances.[7 8] Factors contributing to the development of perinatal depression include poor physical health, limited social support, low economic status, limited education, and history of exposure to violence.[5 9] The covid-19 pandemic placed pregnant people and their families under additional stress, increasing the risk of perinatal mood disorders, including depression.[4 10]

Prenatal depression is a strong predictor of postpartum depression.[11] Mothers with prenatal depression are thus good candidates for interventions that might reduce postpartum depression. Although non-pharmacological measures are preferable,[12] drug treatments are sometimes necessary.[13] Use of traditional antidepressants during pregnancy and

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lactation are limited by delayed onset of effects and potential harm to neonates.[14] Ketamine is a non-competitive N-methyl-D-aspartic receptor antagonist that has long been used for anaesthesia and analgesia.[15] Esketamine is the S-enantiomer of racemic ketamine and has a higher affinity for the N-methyl-D-aspartic receptor than ketamine.[16] Both ketamine and esketamine have rapid onset antidepressant effects,[16 17] although the mechanisms for this remain unclear.[18] Esketamine nasal spray has been approved by the US Food and Drug Administration for treatment resistant depression.[19]

Low dose ketamine or esketamine improves analgesia and relieves depression in mothers having caesarean deliveries.[20-27] However, previous trials were largely restricted to caesarean delivery and excluded mothers with depression and thus at high risk of postpartum depression. We therefore tested the primary hypothesis that a single low dose of esketamine given shortly after delivery reduces depression over 42 days among mothers with prenatal depression.

Methods

Study design

This randomised, double blind, placebo controlled trial with two parallel arms was conducted in five tertiary care hospitals across China. The Biomedical Research Ethics Committee of Peking University First Hospital (2019-336) and other participating centres approved the study protocol (see supplement 1). Written informed consent was obtained from each participant. The trial is reported according to the Consolidated Standards of Reporting Trials guidelines.

Participants

Potential participants were screened with the Edinburgh postnatal depression scale at hospital admission for delivery. This scale is a patient reported 10 item questionnaire used to screen for perinatal depression; scores range from 0 to 30, with higher scores indicating more severe depression.[28] The Chinese version of the Edinburgh postnatal depression scale has been validated, with a score of ≥10 indicating at least mild depression.[29]

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We enrolled pregnant individuals aged 18 years or older with an Edinburgh postnatal depression scale score of ≥10 who were close to childbirth. We excluded those with a prepregnancy history of mood disorders, including depression; communication difficulties; severe complications of pregnancy, such as pre-eclampsia, placenta accreta spectrum, or HELLP (intravascular haemolysis, elevated liver enzymes, and low platelet count) syndrome; American Society of Anesthesiologists physical status III or higher; or any contraindications to ketamine or esketamine, such as refractory hypertension, severe cardiovascular disease, or hyperthyroidism.

Randomisation and masking

An independent biostatistician generated random treatment assignments in a 1:1 ratio, stratified by trial site, with a block size of four using the PROC PLAN procedure of SAS 9.2 software (SAS Institute, Cary, NC). Allocations were sealed in sequentially numbered opaque envelopes controlled by investigators who were otherwise not involved in data acquisition or the participants' care. Coordinators (anaesthesiologist: CW; anaesthesia nurses: G-YG, ML, Y-CL, and C-CH) opened the randomisation envelopes according to the recruitment sequence shortly before the participants gave birth and prepared the appropriate study drugs—either 0.2 mg/kg esketamine diluted in 20 mL normal saline or 20 mL normal saline.

Syringes labelled "trial drug" were given to delivery room nurses for participants having a vaginal delivery or to anaesthesiologists for participants having a caesarean delivery. All participants, healthcare team members, and outcome assessors were therefore fully blinded to treatment. In emergencies such as rapid changes in a participant's clinical status, the delivery room nurses or anaesthesiologists could adjust the speed of infusion or interrupt administration of the study drug. They could also request unmasking if deemed clinically necessary.

Perinatal care and intervention

Routine maternal monitoring included electrocardiography, non-invasive blood pressure measurement, and pulse oximetry, which were performed every one to two hours, or more frequently when necessary. Continuous external fetal heart rate monitoring or tocodynamometry were used as indicated. The participants were given detailed information about the potential benefits and risks of epidural analgesia for labour and decided, in consultation with their healthcare team, whether to have epidural analgesia during labour.

Epidural analgesia for those participants who requested it was initiated when the cervix was dilated at least 1 cm. An epidural catheter was inserted at the L2-L3 or L3-L4 interspace. A 10-15 mL mixture consisting of 0.08-0.13% ropivacaine and 0.36-0.45 µg/mL sufentanil was administered as a loading dose; an additional 5 mL of the mixture was given 10 minutes later if participants' pain score was ≥4 on a numerical rating scale (an 11 point scale where 0=no pain and 10=the worst pain). A participant controlled epidural analgesia pump was attached 30 minutes later, which was established with a mixture of 0.07% ropivacaine and 0.36 µg/mL sufentanil, programmed to deliver an 8 mL bolus with a lockout interval of 30 minutes and an optional background infusion of 4 mL/h. Participant controlled epidural analgesia was discontinued during the second stage of labour, but the background infusion (if used) was continued. Epidural analgesia was usually stopped at the end of the third stage. For participants who did not request neuraxial analgesia, routine perinatal care including intramuscular pethidine was provided.

Obstetric management, including oxytocin and forceps assisted delivery or caesarean delivery was provided or conducted according to routine practice and the corresponding local guidelines. If emergency caesarean delivery was required, epidural anaesthesia was provided by injecting a suitable local anaesthetic dose through an indwelling epidural catheter; otherwise, combined spinal-epidural anaesthesia was used to a target sensory block level from T6 to T4. Vasopressors including ephedrine and phenylephrine were given to maintain blood pressure; opioids including pethidine were administered as supplement analgesia when necessary. Participant controlled epidural or intravenous analgesia was provided for up to 24 hours after caesarean delivery. Infusion of the trial drug (either 0.2 mg/kg esketamine or normal saline) was initiated at a rate of 30 mL/h over a 40 minute period after the umbilical cord was clamped.

Investigator training, data collection, and outcome measures

Before the trial began, investigators responsible for baseline data collection and follow-up assessments (SW, Fei-Xue Wang, TH, TY, H-YZ, and H-MY) were trained by psychiatrists (X-YS and H-NG) to use assessment tools, including the mini-international neuropsychiatric interview (version 6.0.0, depression module) and the 17 item Hamilton depression rating scale. The mini-international neuropsychiatric interview 6.0.0 is a brief structured diagnostic interview to assess depression,[30] and the Chinese version has been validated.[31] Psychiatrists and investigators who were involved in the trial were trained at https://harmresearch.org/ and were certified to diagnose depression with the mini-international neuropsychiatric interview 6.0.0. The Hamilton depression rating scale is a clinician reported scale designed to rate the severity of symptoms observed during major depressive episodes. The scale contains 17 items; possible scores for various items range from 0 to 2 or 0 to 4. The total scores range from 0 to 52, with 0-7 indicating no depression, 8-16 mild depression, 17-23 moderate depression, and ≥24 severe depression.[32] The investigators were trained with a standardised patient and passed a consistency test (see eTable in supplement 2).

Baseline data of the participants were recorded, including personal characteristics, socioeconomic status, pregestational comorbidities, and details of the current pregnancy. Anxiety was assessed with the Zung

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self-rating anxiety scale (scores range from 20 to 80, with higher scores indicating more severe anxiety).[33] Social support was assessed with the social support rating scale (scores range from 11 to 62, with higher scores indicating better social support).[34] Marital satisfaction was assessed with the ENRICH (evaluation and nurturing relationship issues, communication, and happiness) marital satisfaction scale (scores range from 10 to 50, with higher scores indicating better marital satisfaction).[35] The Chinese versions of these instruments have been validated.[36-38]

Maternal data included acceptance of epidural analgesia, mode of delivery, estimated blood loss and fluid infusion, and use of supplemental analgesics and sedatives. Neonatal data included sex, bodyweight, Apgar scores at one and five minutes after birth, and initial destination (eg, postpartum ward, neonatal ward, or neonatal intensive care unit). Certificated investigators or anaesthesiologists supervised infusion of the study drugs. Vital signs including blood pressure, heart rate, oxygen saturation, and agitation-sedation level as assessed with the Richmond agitation-sedation scale (scores range from −5 (unarousable) to 4 (combative) and 0 indicates alert and calm[39]) were recorded every five minutes during infusion of the study drug and every 10 minutes thereafter for 60 minutes. Thus, every participant was monitored for one hour after the study drug had been administered and before being transferred to a ward.

We conducted a face-to-face interview with the mothers between 18 and 30 hours after childbirth. Participants were also contacted by telephone on the seventh postpartum day and were contacted again on day 42 for face-to-face or online video interviews. Pain intensity was assessed with the numerical rating scale (an 11 point scale where 0=no pain and 10=the worst pain), with a difference of ≥1 point being considered clinically meaningful.[40] Breastfeeding was recorded as exclusive, mixed, or none. Symptoms of depression were assessed with the Edinburgh postnatal depression scale score at seven and 42 days post partum; an improvement of at least 4 points or worsening of at least 3 points was considered clinically meaningful.[41] Depression was also assessed with the depression module of the mini-international neuropsychiatric interview 6.0.0 and the Hamilton depression rating scale at 42 days; the assessments were supervised by psychiatrists for the first two participants and then one in every 10 participants at each study centre. Supervision was performed by examining the recorded video or audio files during the assessment process. As a result, assessments of 43 participants were reviewed, with diagnoses confirmed by psychiatrists.

Our primary endpoint was the prevalence of a major depressive episode at 42 days post partum, diagnosed using the mini-international neuropsychiatric interview 6.0.0.[30 31] Participants with a diagnosis of major depressive episode were advised to visit mental health facilities for further consultation. Predefined secondary endpoints post partum included Edinburgh postnatal depression scale scores at seven and 42 days; Hamilton depression rating scale score at 42 days; numerical rating scale of pain and proportion with exclusive breastfeeding at one, seven, and 42 days; length of hospital stay; and maternal and neonatal complications within 42 days after childbirth. Maternal and neonatal complications were defined as any medical conditions that required hospital visits and treatment intervention.

Prespecified adverse events were monitored continuously during and for an hour after infusion of the study drug, two hours after infusion, and on the first postpartum day. Specifically, we monitored tachycardia (heart rate >100 beats/min), hypertension (systolic blood pressure >160 mm Hg or an increase >30% from baseline), respiratory depression (respiratory rate <10 breaths per minute), desaturation (oxygen saturation <90% or an absolute decrease of >5% from baseline), sedation (Richmond agitation-sedation scale ≤−2), somnolence, and nausea or vomiting, as well as neuropsychiatric symptoms such as dizziness, agitation (Richmond agitation-sedation scale ≥2), diplopia, hallucinations, and daymares or nightmares. We also monitored other side effects, including stomach ache and leg numbness. Side effects were managed according to local routine, including intravenous midazolam when considered necessary (see supplement 1).

Statistical analysis

Sample size estimation

As with previous studies, we estimated the prevalence of postpartum depression to be 42-50% in women with prenatal depression.[42 43] In a trial of patients with treatment resistant depression, the response rate was 67% after 0.2 mg/kg of intravenous esketamine.[44] We therefore assumed that the prevalence of depression at 42 days post partum would be 45%, and that treatment with low dose esketamine would decrease depression by about one third. With a two sided significance level set at 0.05 and power at 80%, we determined that 328 participants would be required to detect such a difference. We expected a dropout rate of about 10% and thus planned to enrol a total of 364 participants.

Data analyses

Outcome analyses were primarily performed in the intent-to-treat population—that is, all participants were analysed in the group to which they were randomly assigned. For the primary endpoint, we also conducted a per protocol analysis after excluding those with protocol deviations or who withdrew consent.

The prevalence of a major depressive episode at 42 days post partum, our primary endpoint, was compared with a χ^2 test, with differences between groups expressed as relative risk and 95% confidence interval (CI). The number needed to treat was estimated as the reciprocal of the absolute risk reduction. Prespecified subgroup analyses were performed using logistic regression models to calculate the treatment-by-covariate interactions. As a post hoc sensitivity analysis, we imputed missing primary endpoint data. As the proportion of participants with missing data was <5%, we assigned best outcome to participants in the placebo group and worst outcome to participants in the esketamine group.[45]

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For secondary and other endpoints, we analysed continuous variables using a *t* test or Mann-Whitney test. Median differences (and 95% CIs) were calculated with Hodges-Lehmann estimators. Categorical variables were analysed with χ^2 test, continuity corrected χ^2 tests, or Fisher's exact test. Relative risks (and 95% CIs) were calculated. Time-to-event data were evaluated with Kaplan-Meier survival analysis, with between group difference tested with the log-rank test. Hazard ratios (and 95% CIs) were estimated from a Cox proportional hazard model. Missing data were not replaced.

On an exploratory basis, for the Edinburgh postnatal depression rating scale we estimated the percentages of scores ≤9, reduction in score ≥4 points from baseline, and reduction in score ≥50% from baseline at seven and 42 days post partum, along with the percentage of Hamilton depression rating scale scores ≤7 at 42 days post partum. We also compared primary and key secondary endpoints in participants with or without side effects and in those with or without neuropsychiatric symptoms.

For hypothesis testing, we considered a two tailed P value of <0.05 to be statistically significant. For subgroup treatment-by-covariate interactions, we considered P<0.10 to be statistically significant. Statistical analyses were performed with the SPSS 25.0 software (IBM SPSS, Chicago, IL).

Patient and public involvement

Mothers close to childbirth with prenatal depression were involved in our previous pilot trial and reviewed questionnaire for the present study.[43] At the protocol stage, we gained opinions from participating medical centres on the content of follow-ups.

Results

Patient population

From 19 June 2020 to 21 June 2022, a total of 14 243 women were screened for inclusion. Among these, 479 were eligible and 364 were enrolled and randomised to receive either esketamine (n=182) or placebo (n=182). All enrolled participants were given an infusion of the study drug. During the postpartum follow-up period, two participants in the esketamine group and one participant in the placebo group withdrew consent. Therefore, all 364 participants were included in the intention-to-treat analysis and 361 participants were

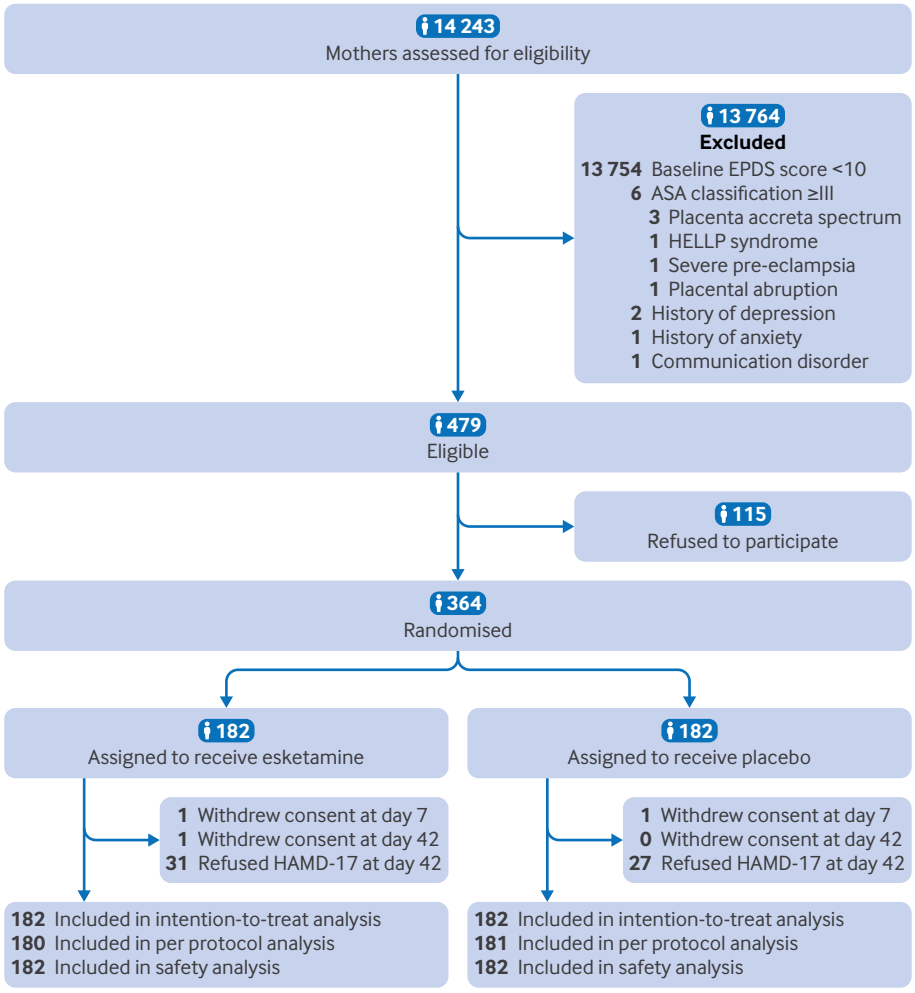


Fig 1 | Flow of participants through trial. ASA=American Society of Anesthesiologists; EPDS=Edinburgh postnatal depression scale; HAMD-17=17 item Hamilton depression rating scale; HELLP=intravascular haemolysis, elevated liver enzymes, and low platelet count syndrome

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included in the per protocol analysis (fig 1; also see eTable 2 in supplement 2). The last participant was followed-up on 3 August 2022.

The mean age of enrolled participants was 31.8 (SD 4.1) years. Table 1 presents the baseline personal and clinical characteristics of the participants. Intrapartum data, including those of the mothers and neonates, were similar in each treatment group (table 2). No participant took oral antidepressants or received psychotherapy between childbirth and 42 postpartum days.

Table 1 | Baseline data of participants with prenatal depression assigned to receive esketamine or placebo immediately after delivery. Values are numbers (percentages) unless stated otherwise

Variables	Esketamine (n=182)	Placebo (n=182)
Maternal data		
Mean (SD) age (years)	31.8 (4.0)	31.7 (4.1)
Mean (SD) prenatal body mass index	27.0 (3.6)	27.0 (3.7)
Duration of education (years):		
‹9	8 (4.4)	4 (2.2)
9-12	19 (10.4)	9 (4.9)
›12	155 (85.2)	169 (92.9)
Full time employment	150 (82.4)	157 (86.3)
Family income (Chinese Yuan/month):		
‹10000	15 (8.2)	16 (8.8)
10000-20000	64 (35.2)	68 (37.4)
20001-40000	76 (41.8)	69 (37.9)
›40000	27 (14.8)	29 (15.9)
Covered by social health insurance	172 (94.5)	167 (91.8)
Stressful life events within 2 years*	21 (11.5)	19 (10.4)
Pregestational condition:		
Medical comorbidities†	29 (15.9)	30 (16.5)
Gynaecological diseases‡	40 (22.0)	44 (24.2)
Dysmenorrhoea	85 (46.7)	76 (41.8)
Premenstrual syndrome§	22 (12.1)	19 (10.4)
History of surgery	58 (31.9)	58 (31.9)
History of adverse pregnancy outcome¶	58 (31.9)	66 (36.3)
Pregnancy:		
Planned	133 (73.1)	127 (69.8)
Routine antenatal care	178 (97.8)	181 (99.5)
Childbirth classes	103 (56.6)	106 (58.2)
Obstetric diseases**	49 (26.9)	52 (28.6)
Low back pain affecting daily life††	73 (40.1)	60 (33.0)
Median (IQR) No of pregnancies	1 (1-2)	1 (1-2)
Median (IQR) No of deliveries	0 (0-1)	0 (0-1)
Median (IQR) gestational age (days)	273 (267-279)	274 (269-280)
Twin pregnancy	7 (3.8)	3 (1.6)
Mean (SD) prepartum haemoglobin (g/L)	119.6 (11.4)	120.4 (11.8)
Median (IQR) Edinburgh postnatal depression scale‡‡	10 (10 to 12)	10 (10 to 12)
Median (IQR) Zung self-rating anxiety scale§§	36 (32 to 41)	36 (32 to 41)
Median (IQR) social support rating scale¶¶	39 (35 to 44)	41 (36 to 45)
Median (IQR) ENRICH marital satisfaction scale***	41 (38 to 46)	42 (38 to 47)
Paternal data		
Smoking	50 (27.5)	55 (30.2)
Alcohol intake	70 (38.5)	62 (34.1)
Education ›12 years	161 (88.5)	162 (89.0)
Full time employment	172 (94.5)	173 (95.1)
Study sites		
Site 1	106 (58.2)	106 (58.2)
Site 2	30 (16.5)	30 (16.5)
Site 3	24 (13.2)	24 (13.2)
Site 4	22 (12.1)	22 (12.1)
Site 5	0	0

1Chinese Yuan=£0.11; €0.13.
*Bereavement, unintentional injury, divorce, and unemployment.
†Asthma, interstitial lung disease, arrhythmia, latent glomerulonephritis, polycystic kidney disease, nephrotic syndrome, systemic lupus erythematosus, L-carnitine deficiency, and positive hepatitis B surface antigen.
‡Hysteromyoma, ovarian cysts, dysfunctional uterine bleeding, polycystic ovary syndrome, and pelvic inflammatory disease.
§Consistent pattern of emotional and physical symptoms occurring only during the luteal phase of the menstrual cycle that are of enough severity to interfere with some aspects of life. Diagnosis was made by gynaecologists.
¶Miscarriage, induced abortion, ectopic pregnancy, and mid-trimester induction of labour due to fetal anomalies.
**Impaired glucose tolerance or gestational diabetes mellitus, pregnancy induced hypertension syndrome or pre-eclampsia, low free triiodothyronine or free thyroxine, or both, vulvovaginal candidiasis, antiphospholipid syndrome, cervical incompetence, and cholestasis in pregnancy.
††One of the following activities affected: walking, mood, sleep, or concentration, as judged by participants themselves.
‡‡Range 0-30, with higher scores indicating more severe depression.
§§Range 20-80, with higher scores indicating more severe anxiety.
¶¶Range 11-62, with higher scores indicating better social support.
***Range 10-50, with higher scores indicating better marital satisfaction.

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Table 2 | Perinatal data for participants with prenatal depression assigned to receive esketamine or placebo immediately after delivery

Variables	Esketamine (n=182)	Placebo (n=182)	P value
Maternal data			
Epidural labour analgesia	81 (44.5)	88 (48.4)	0.46
In women scheduled for vaginal delivery	81 (68.6) (n=118)	88 (66.7) (n=132)	0.74
Mode of delivery:			0.39
Elective caesarean delivery	64 (35.2)	50 (27.5)	
Emergent caesarean delivery	24 (13.2)	27 (14.8)	
Forceps delivery	18 (9.9)	16 (8.8)	
Spontaneous delivery	76 (41.8)	89 (48.9)	
Maximal temperature during labour*	(n=94)	(n=105)	
≥38°C	3 (3.2)	2 (1.9)	0.67
>37.5°C	9 (9.6)	14 (13.3)	0.41
Median (IQR) fluid infusion (mL)	1000 (500-1100)	1000 (500-1500)	0.63
Median (IQR) estimated blood loss (mL)	300 (285-400)	300 (300-400)	0.43
Use of analgesics or sedatives†	17 (9.4)	18 (9.9)	>0.99
Median (IQR) time to first ambulation (h)	6 (4-16)	7 (4-14)	0.97
Post-vaginal delivery	4 (3-6)	4 (3-8)	0.39
Post-caesarean delivery	13 (8-24)	12 (8-21)	0.80
Median (IQR) time to first breastfeeding (h)	4 (2-18) (2)‡	3 (1-19) (2)‡	0.36
Post-vaginal delivery	3 (1-12) (2)‡	3 (1-16) (1)‡	0.69
Post-caesarean delivery	6 (2-24)	4 (1-23) (1)‡	0.11
Neonatal data§	(n=189)	(n=185)	
Male sex	104 (55.0)	105 (56.8)	0.74
Sex consistent with father's preference	165 (87.3)	161 (87.0)	0.63
Sex consistent with mother's preference	159 (84.1)	152 (82.2)	0.61
Mean (SD) birthweight (g)	3180.5 (488.0)	3249.0 (487.4)	0.18
Apgar score:			
Median (IQR) at 1 minute	10 (10-10)	10 (10-10)	0.37
<7 at 1 minute	3 (1.6)	5 (2.7)	0.50
Median (IQR) at 5 minutes	10 (10-10)	10 (10-10)	0.75
<7 at 5 minutes	0	0	—
First destination after birth:			0.83
Postpartum ward	152 (80.4)	153 (82.7)	
Neonatal ward¶	28 (14.8)	25 (13.5)	
Neonatal intensive care unit**	9 (4.8)	7 (3.8)	

*Among women who gave vaginal delivery.
†Included pethidine, nalbuphine, dezocine, pentazocine, butorphanol, tramadol, and phenobarbital. Merged to avoid identifiability.
‡Patients with missing data.
§Includes 10 twin pregnancies.
¶Indications included intrauterine asphyxia, hypoglycaemia, neonatal malformation, neonatal infection, maternal syphilis, and premature delivery.
**Indications included intrauterine asphyxia, hypoxic ischaemic encephalopathy, neonatal infection, and premature delivery.

Efficacy outcomes

Our primary endpoint, a major depressive episode at 42 days post partum, was observed in 6.7% (12/180) of participants in the esketamine group compared with 25.4% (46/181) in the placebo group (relative risk 0.26, 95% CI 0.14 to 0.48; P<0.001; number needed to treat 5, 95% CI 4 to 9). After missing data had been imputed, major depressive episodes occurred in 7.7% (14/182) of participants in the esketamine group compared with 25.3% (46/182) in the placebo group (relative risk 0.30, 95% CI 0.17 to 0.53; P<0.001; table 3). The results of per protocol analyses were similar. No significant interactions were observed between predefined subgroups and the exposure-outcome association on the multiplicative scale (see eFig 1 in supplement 2).

Edinburgh postnatal depression scale scores were lower in the esketamine group at seven days (median difference −3, 95% CI −4 to −2; P<0.001) and 42 days post partum (−3, −4 to −2; P<0.001; see eFig 2 in supplement 2). Hamilton depression rating scale scores at 42 days post partum were also lower in the esketamine group (median difference −4, −6 to −3; P<0.001). The numerical rating scale scores for pain were lower in the esketamine group on the first post-delivery day (at rest: median difference −1, −1 to 0; P=0.003; with movement: median difference −1, −1 to 0; P=0.001), at seven days (median difference −1, −1 to 0; P=0.003), and at 42 days post partum (0, 0 to 0; P=0.04). The proportion of mothers with persistent pain at 42 days was also lower in the esketamine group (35.2% (63/179)) than the placebo group (47.5% (86/181)): relative risk 0.74, 95% CI 0.58 to 0.95; P=0.02. Other outcomes did not differ significantly between the groups, including the proportion of mothers who were exclusively breastfeeding at one, seven, and 42 days post partum (table 3).

In exploratory analyses, the proportion of participants with Edinburgh postnatal depression scale scores of ≤9 was higher in the esketamine group at seven days (relative risk 1.49, 95% CI 1.29 to 1.71; P<0.001) and at 42 days (1.43, 1.25 to 1.65; P<0.001). The proportion of participants with reduction in Edinburgh postnatal depression scale scores of ≥4 from baseline was higher

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Table 3 | Efficacy outcomes in participants with prenatal depression assigned to receive esketamine or placebo immediately after delivery

Outcomes by postpartum days	Esketamine (n=182)	Placebo (n=182)	Estimated effects (95% CI)*	P value
Primary endpoint				
Major depressive episode at 42 days†	12 (6.7) (2)‡	46 (25.4) (1)‡	Relative risk: 0.26 (0.14 to 0.48)	**<0.001**
Major depressive episode at 42 days (missing data imputed)†§	14 (7.7)	46 (25.3)	Relative risk: 0.30 (0.17 to 0.53)	**<0.001**
Secondary endpoints				
Median (IQR) Edinburgh postnatal depression scale score at 7 days¶	5 (2 to 8) (1)‡	9 (5 to 11) (1)‡	Median difference: −3 (−4 to −2)	**<0.001**
Median (IQR) Edinburgh postnatal depression scale score at 42 days¶	5 (3 to 8) (2)‡	8 (5 to 11) (1)‡	Median difference: −3 (−4 to −2)	**<0.001**
Median (IQR) Hamilton depression rating scale score at 42 days**	5 (2 to 8) (33)‡	10 (5 to 17) (28)‡	Median difference: −4 (−6 to −3)	**<0.001**
Median (IQR) length of hospital stay after delivery (days)	4 (3 to 5) (1)‡	4 (3 to 4) (1)‡	Hazard ratio: 1.04 (0.85 to 1.28)	0.82
Median (IQR) numerical rating scale for pain††:				
At 1 day				
At rest	2 (1 to 3)	2 (1 to 3) (1)‡	Median difference: −1 (−1 to 0)	**0.003**
With movement	3 (2 to 5)	4 (3 to 6) (1)‡	Median difference: −1 (−1 to 0)	**0.001**
At 7 days	1 (0 to 3) (1)‡	2 (1 to 3) (1)‡	Median difference: −1 (−1 to 0)	**0.003**
At 42 days	0 (0 to 2) (3)‡	0 (0 to 2) (1)‡	Median difference: 0 (0 to 0)	**0.04**
Persistent pain at 42 days‡‡	63 (35.2) (3)‡	86 (47.5) (1)‡	Relative risk: 0.74 (0.58 to 0.95)	**0.02**
Exclusive breastfeeding:				
At 1 day	97 (53.3)	94 (51.6)	Relative risk: 1.03 (0.85 to 1.26)	0.75
At 7 days	83 (45.9) (1)‡	76 (42.0) (1)‡	Relative risk: 1.10 (0.87 to 1.39)	0.43
At 42 days	84 (46.7) (2)‡	78 (43.1) (1)‡	Relative risk: 1.08 (0.86 to 1.36)	0.50
Maternal complications within 42 days§§	18 (10.0) (2)‡	21 (11.6) (1)‡	Relative risk: 0.86 (0.48 to 1.56)	0.62
Neonatal complications within 42 days¶¶	28 (15.6) (2)‡	32 (17.7) (1)‡	Relative risk: 0.88 (0.55 to 1.40)	0.59
Exploratory analysis				
Edinburgh postnatal depression scale score ≤9¶:				
At 7 days	153 (84.5) (1)‡	103 (56.9) (1)‡	Relative risk: 1.49 (1.29 to 1.71)	**<0.001**
At 42 days	151 (83.9) (2)‡	106 (58.6) (1)‡	Relative risk: 1.43 (1.25 to 1.65)	**<0.001**
Reduction of Edinburgh postnatal depression scale score ≥4 from baseline¶:				
At 7 days	134 (74.0) (1)‡	82 (45.3) (1)‡	Relative risk: 1.63 (1.36 to 1.96)	**<0.001**
At 42 days	133 (73.9) (2)‡	78 (43.1) (1)‡	Relative risk: 1.72 (1.42 to 2.07)	**<0.001**
Reduction of Edinburgh postnatal depression scale score ≥50% from baseline¶:				
At 7 days	112 (61.9) (1)‡	50 (27.6) (1)‡	Relative risk: 2.24 (1.72 to 2.91)	**<0.001**
At 42 days	98 (54.4) (2)‡	54 (29.8) (1)‡	Relative risk: 1.83 (1.41 to 2.37)	**<0.001**
Hamilton depression rating scale score ≤7 at 42 days**	106 (71.1) (33)‡	60 (39.0) (28)‡	Relative risk: 1.83 (1.46 to 2.28)	**<0.001**

P values in bold indicate <0.05.
CI=confidence interval; IQR=interquartile range.
*Calculated as esketamine group minus or compared with placebo group.
†Diagnosed using the mini-international neuropsychiatric interview version 6.0.0. Missing data owing to consent withdrawn.
‡Participants with missing data owing to consent withdrawn or refused assessment.
§For patients with missing data, those administered placebo were assigned best outcome (no postpartum depression), whereas those administered esketamine were assigned worst outcome (developed postpartum depression).
¶Range 0-30 with higher scores indicating more severe depression.
**Range 0-52, with higher scores indicate more severe depression. Scores ≤7 indicate no depression.
††Range 0-10, with 0 representing no pain and 10 representing the worst pain.
‡‡Defined as the numerical rating scale score for pain ≥1 that persisted from childbirth.
§§Those who required treatment intervention and included mastitis, facioplegia, puerperal infection, and eczema.
¶¶Those who required treatment intervention and included respiratory distress syndrome, pneumonia, omphalitis, hyperbilirubinaemia, neonatal jaundice, dysplasia of hip joint, and eczema.

in the esketamine group (at seven days: relative risk 1.63, 1.36 to 1.96; P<0.001; at 42 days: 1.72, 1.42 to 2.07; P<0.001). The proportion of participants with reductions in Edinburgh postnatal depression scale scores of ≥50% from baseline was also higher in the esketamine group (at seven days: 2.24, 1.72 to 2.91; P<0.001; at 42 days: 1.83, 1.41 to 2.37; P<0.001). The proportion of participants with Hamilton depression rating scale scores ≤7 at 42 days was higher in the esketamine group (1.83, 1.46 to 2.28; P<0.001; table 3). No significant interactions were found between the presence of adverse events or neuropsychiatric adverse events and the exposure-outcome associations (see eTables 3 and 4 in supplement 2).

Safety outcomes

During and within one hour after infusion of the study drug, blood pressure, heart rate, and oxygen saturation were similar in each group. Richmond agitation-sedation scores were lower in the esketamine group from 20 minutes after initiating study drug infusion until 20 minutes after the end of study drug infusion, but the differences were not clinically meaningful (median differences 0, 95% CI 0 to 0; P≤0.017; see eTables 5 and 6 in supplement 2). Participants in the esketamine group were more often sedated (5.5% (10/182) *v* 0.5% (1/182); P=0.006), reported fewer stomach aches (1.1% (2/182) *v* 5.5% (10/182); P=0.02), and had more neuropsychiatric symptoms (33.5% (61/182) *v* 11.0% (20/182); P<0.001), including more dizziness (26.4% (48/182) *v* 9.3% (17/182); P<0.001), more diplopia (4.9% (9/182) *v* 0% (0/182); P=0.004), and more hallucinations or daymares (3.3% (6/182) *v* 0% (0/182); P=0.03). About a 10th of participants in the esketamine group required transient interruptions to study drug infusion owing to dizziness (10.4% (19/182) *v* 0% (0/182); P<0.001), but none required other interventions, including midazolam; study drug infusion was restarted about 20 minutes later and completed in all participants. Five mothers reported

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Table 4 | Adverse events in participants with prenatal depression assigned to receive esketamine or placebo immediately after delivery

	No (%)	
	Esketamine (n=182)	Placebo (n=182)
During and within 1 hour after study drug infusion		
Tachycardia*	16 (8.8)	13 (7.1)
Hypertension†	1 (0.5)	0
Sedation‡	10 (5.5)	1 (0.5)
Somnolence	4 (2.2)	1 (0.5)
Nausea or vomiting	4 (2.2)	9 (4.9)
Stomach ache	2 (1.1)	10 (5.5)
Neuropsychiatric symptoms	61 (33.5)	20 (11.0)
Dizziness	48 (26.4)	17 (9.3)
Study drug interruption§	19 (10.4)	0
Diplopia	9 (4.9)	0
Hallucination or daymare¶	6 (3.3)	0
Agitation**	6 (3.3)	5 (2.7)
At 2 hours after study drug infusion		
Somnolence	3 (1.6)	0
Nausea or vomiting	8 (4.4)	14 (7.7)
Neuropsychiatric symptoms	37 (20.3)	24 (13.2)
Dizziness	32 (17.6)	24 (13.2)
Diplopia	4 (2.2)	0
Hallucination or daymare¶	3 (1.6)	0
Postpartum day 1		
Nausea or vomiting	5 (2.7)	7 (3.8)
Leg numbness	2 (1.1)	7 (3.8)

*Heart rate >100 beats per minute.
†Systolic blood pressure >160 mm Hg or an increase of >30% from baseline.
‡Richmond agitation sedation scale score ≤−2 during drug infusion.
§Study drug infusion was stopped transiently owing to dizziness.
¶Merged to avoid identifiability.
**Richmond agitation sedation scale score ≥2 during drug infusion.

hallucinations during and within an hour after infusion of the study drug; the hallucinatory symptoms lasted for two hours in two participants. Two hours after infusion of the study drug, the prevalence of adverse events, including neuropsychiatric adverse events, did not significantly differ between the two groups. No neuropsychiatric symptoms were observed on the first postpartum day (table 4).

The overall incidence of neuropsychiatric adverse events was higher in the esketamine group (45.1% (82/182) *v* 22.0% (40/182); P<0.001). No severe adverse events occurred during the study period.

Discussion

For mothers with prenatal depression, a single low dose of esketamine given immediately after childbirth reduced the prevalence of major depressive episode at 42 days post partum by about three quarters, with a number needed to treat of 5. Participants in the esketamine group had lower Edinburgh postnatal depression scale scores at seven and 42 days post partum, and a lower Hamilton depression rating scale score at 42 days post partum. The antidepressant effect of low dose esketamine thus seems to last longer in mothers with prenatal depression than in the general population with depression.[19 46] A reasonable supposition is that depression in perinatal mothers is typically less severe than in previous non-obstetrical trials, which were often conducted in people with severe or even treatment resistant depression.[19 46 47] Whether the response to esketamine persists beyond 42 days requires further investigation.

Comparison with other studies

Our results were generally consistent with previous work investigating the effects of low dose ketamine[21 22] or esketamine on postpartum depression, mainly in mothers after caesarean delivery.[23-27] In a retrospective analysis of 240 mothers close to childbirth, esketamine administered for postoperative analgesia (mean 0.35 mg/kg during a 24 hour period) was associated with lower Edinburgh postnatal depression scale scores at three months.[24] In a trial of 375 mothers about to give birth, esketamine given by way of patient controlled intravenous analgesia (at a rate of 0.25 mg/kg/day) for 48 hours lowered the prevalence of depression by 60% at 14 days.[25] Two small trials reported that a single intraoperative dose of esketamine (0.2 or 0.5 mg/kg) decreased the prevalence of depression at 42 days by 73% and 58%, respectively.[23 26] Two other trials enrolled patients with Edinburgh postnatal depression scale scores of ≥10; one found that perioperative esketamine (0.25 mg/kg intraoperatively followed by 1-2 mg/kg postoperatively over 48 hours) reduced the prevalence of depression by 63% to 76% at seven days and by 49% to 67% at 42 days after caesarean delivery[27]; another study reported that intraoperative esketamine (0.3 mg/kg) lowered Edinburgh postnatal depression scale scores at seven and 42 days after curettage surgery.[48]

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Among available studies, primary endpoints (postpartum depression) were mainly diagnosed according to the Edinburgh postnatal depression scale, usually with a cut-off value of ≥10.[20-25 27] However, the Edinburgh postnatal depression scale is designed for screening rather than diagnosis, and the cut-off threshold score of ≥10 provides insufficient specificity for diagnosing perinatal depression compared with reference standards.[49] Two recent trials investigating the effects of low dose esketamine reported neutral results.[50 51] We noted that in one trial perioperative esketamine (0.25 mg during caesarean delivery and 1.25 mg/kg postoperatively for about 48 hours) decreased depression (defined as Edinburgh postnatal depression scale scores ≥13) by 34% at three days and by 38% at 42 days; the decreases were clinically important but not statistically significant owing to limited sample size.[50] In another trial, depression (defined as Edinburgh postnatal depression scale scores ≥9) at one week post partum occurred in only 4% (4/102) of mothers given esketamine (0.25 mg/kg) and in 2% (2/100) of mothers given placebo, possibly owing to exclusion of high risk mothers; this meant the trial was seriously underpowered to detect between group differences.[51]

Importantly, our trial extends existing understanding by targeting women with pre-existing prenatal depression, who were therefore at high risk of postnatal depression. In contrast, most previous trials generally recruited participants who were healthy, and some even excluded those with prenatal depression or mental disorders.[22 25 50 51] The prevalence of postnatal depression was high in our selected population, although not as high as we expected. Selecting participants with baseline depression resulted in a low number needed to treat, which depends on baseline incidence. Targeting mothers most likely to benefit also limited side effects to those most likely to benefit, thus providing a favourable risk-benefit ratio.

Side effects of low dose esketamine depend on the rate it is administered. For example, at most, 98% of participants developed neurological or mental symptoms when 0.25 mg/kg esketamine was injected intravenously over one minute[52]; the proportion was lower when low dose esketamine was infused over 40 minutes.[44] Our results are consistent with previous reports, which indicate that a single low dose of esketamine (0.2-0.25 mg/kg) infused over 40 minutes is generally well tolerated in people with treatment resistant depression.[44 53] We did not find a significant correlation between neuropsychiatric symptoms and antidepressant effects of esketamine in the present study, which was in line with previously reported results.[54] Further work is, however, needed because the literature remains inconsistent.[55]

Additional findings

In the present study, the prevalence of prenatal depression (defined as Edinburgh postnatal depression scale scores ≥10) was only 3%, which is much less than in our previous studies and reported elsewhere.[2 9 56 57] This might be due to depression screening and psychological interventions that have become routine parts of prenatal care in the Beijing area since June 2020 and reduced the amount of prenatal depression at the time of delivery.[58] Consistent with this theory, the prevalence of prenatal depression was 2% (285/12 780) among women recruited in Beijing and 14% (204/1463) among those recruited in other cities.

The analgesic effect of esketamine may last for several hours after use, or even longer. A recent meta-analysis reported that adults given esketamine during general anaesthesia had improved analgesia for up to 24 hours and reduced morphine consumption for up to 12 hours after surgery.[59] Therefore, as might be expected, participants in the esketamine group in the present study reported meaningfully lower pain scores while resting and with movement on the first postpartum day. Furthermore, participants in the esketamine group had lower pain scores seven days and 42 days post partum, although the improvements were small. Participants in the esketamine group also reported less persistent pain at 42 days post partum. The mechanisms underlying improved analgesia seven and 42 days post partum remain unclear. Severe acute pain is, however, strongly associated with persistent pain, an effect thought to be at least partially mediated by activation of N-methyl-D-aspartic receptors.[60] Another potential mechanism is that depression and persistent pain are highly intertwined and may well exacerbate each other.[61]

Limitations of this study

An important limitation is that we excluded mothers with prepregnancy mood disorders (three mothers were excluded for depression or anxiety), and thus failed to include participants in greatest need of intervention. The potential moderating effect of a history of mood disorder should be considered when interpreting our results for reduction in symptoms, decrease in prevalence, and longer term wellbeing of individuals after childbirth. A further limitation is the lack of standardised assessment tools and a data safety monitoring board as well as the short monitoring period for neuropsychiatric symptoms and other adverse events, which might lead to an under-reporting of the true extent. Owing to exclusion of individuals with previous mood disorders and possibly underestimated adverse effects, the broader issue of the external validity and generalisability of the benefit:risk ratio is much constrained. Thirdly, we did not evaluate the participants' impression on type of drug they received. It can be argued that trials investigating psychedelic drugs might over-estimate treatment effects owing to unblinding of participants and high levels of response expectancy.[62] However, we found no significant interactions between the presence of adverse events or neuropsychiatric adverse events and the exposure-outcome associations in our results. Lastly, with a median baseline Edinburgh postnatal depression scale score of 10 (interquartile

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range 10-12), most participants in our trial had only mild prenatal depression. Whether esketamine is equally effective in pregnant mothers with more severe depression remains to be determined.

Conclusions

In mothers with prenatal depression, a single low dose infusion of esketamine shortly after delivery reduced major depressive episodes at 42 days post partum by about three quarters. Neuropsychiatric adverse events were more frequent but transient and did not require drug treatment. Low dose esketamine should be considered in mothers with symptoms of prenatal depression.

AUTHOR AFFILIATIONS

[1]Department of Anaesthesiology, Peking University First Hospital, Beijing 100034, China

[2]Department of Anaesthesiology, Women's Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China

[3]Department of Anaesthesiology, Hunan Province Maternal and Child Health Care Hospital, Changsha, Hunan Province, China

[4]Department of Anaesthesiology, Women's Hospital of Nanjing Medical University, Nanjing Maternity and Child Health Care Hospital, Nanjing, Jiangsu Province, China

[5]Peking University Sixth Hospital, Peking University Institute of Mental Health, NHC Key Laboratory of Mental Health (Peking University), National Clinical Research Centre for Mental Disorders (Peking University Sixth Hospital), Beijing, China

[6]Department of Outcomes Research, Cleveland Clinic, Cleveland, OH, USA

[7]Outcomes Research Consortium, Cleveland, OH, USA

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Contributors: SW and C-MD contributed equally to this work. YZ and D-XW conceived the study. SW, C-MD, YZ, X-ZC, A-YL, S-WF, L-LX, X-YS, H-NG, and D-XW designed the study. SW, ZY, L-LX, LC, H-MY, HH, TY, TH, H-YZ, MJ, X-YS, and H-NG conducted the study. ZY, X-ZC, A-YL, S-WF, X-YS, H-NG, and D-XW coordinated and supervised the study. SW and C-MD conducted analyses. SW, C-MD, ZY, X-ZC, A-YL, S-WF, X-YS, H-NG, DIS, and D-XW interpreted the results. SW and C-MD wrote the first draft of the manuscript. DIS and D-XW critically revised the manuscript. All authors approved the final version. SW and C-MD had full access to all data and take responsibility for the integrity of the data and the accuracy of the data analysis. D-XW is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: The study protocol was approved by the Biomedical Research Ethics Committee of Peking University First Hospital (2019(336)) and other participating centres.

Data sharing: Anonymised individual patient data can be made available to researchers who provide a sound proposal and ethical approval, considering possible legal restrictions of China. Requests should be sent to corresponding author (wangdongxin@hotmail.com or dxwang65@bjmu.edu.cn).

Transparency: The lead author (D-XW) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Dissemination to participants and related patient and public communities: As the personal identifying information of participants has been removed from the study dataset, it is not possible to send the results of this study to participants. Findings will be shared with clinicians and patients through national and international conferences and press release.

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Supplementary information: Supplement 1: trial protocol and statistical analysis plan
Supplementary information: Supplement 2: supplementary online content

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