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Esketamine administered epidurally as an adjuvant to epidural ropivacaine for labour analgesia: a prospective, double-blind dose-response study

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ABSTRACT

Objective To investigate the efficacy of esketamine as an adjuvant to epidural ropivacaine for labour analgesia by determining its effect on the median effective concentration (EC_{50}) in a 20 ml volume of ropivacaine.

Design A prospective, double-blind dose-response study.

Setting This study was conducted in Women's Hospital, School of Medicine, Zhejiang University, China.

Participants One hundred and fifty parturients who requested epidural analgesia were recruited in this study to randomly receive epidural ropivacaine alone or with esketamine of 0.2 mg ml^{-1}, 0.3 mg ml^{-1}, 0.4 mg ml^{-1} or 0.5 mg ml^{-1}, respectively.

Primary and secondary outcome measures The primary outcome, EC_{50} of ropivacaine, was determined using an up-down sequential allocation technique. The secondary outcomes were analgesia characteristics, Ramsay Sedation Scale score, labour duration, caesarean section rate and adverse effects.

Results The EC_{50} of ropivacaine with the addition of esketamine at concentrations of 0.3 mg ml^{-1}, 0.4 mg ml^{-1} and 0.5 mg ml^{-1} resulted in significant reductions in the EC_{50} of ropivacaine to 0.050%, 0.044% and 0.043%, respectively, from baseline (esketamine 0 mg ml^{-1}) ($p<0.0001$). However, reductions of the EC_{50} of ropivacaine were similar among the groups with esketamine of 0.3 mg ml^{-1}, 0.4 mg ml^{-1} and 0.5 mg ml^{-1} ($p>0.05$). The Ramsay Sedation Scale score was higher and more dizziness was observed in the Group of esketamine 0.5 mg ml^{-1} compared with all other groups ($p<0.0001$). During the peripartum period, no differences in sensory blockade level, Bromage score, labour duration and percentage of caesarean delivery were found among the groups.

Conclusions Under the conditions of this study, the addition of epidural esketamine of 0.3 mg·mL^{-1}, 0.4 mg·mL^{-1} and 0.5 mg·mL^{-1} offered a similar ropivacaine dose-sparing effect; 0.5 mg·mL^{-1} of esketamine produced more adverse effects.

Trial registration number ChiCTR2100054348.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective, double-blind dose-response study quantified the ropivacaine-sparing effect of epidural esketamine at different doses by determining its effect on the median effective concentration (EC_{50}) of ropivacaine, as well as potential maternal and neonatal adverse effects in parturients receiving epidural labour analgesia.

⇒ The clinical trial also investigated the safety of esketamine as an adjuvant to epidural ropivacaine for labour analgesia by comparing potential maternal and neonatal adverse effects of five different concentrations of epidural esketamine.

⇒ However, the ropivacaine-sparing effects of esketamine were determined by EC_{50} using an up-down sequential allocation technique other than EC95 of ropivacaine.

⇒ Because supplemental esketamine was used only as an initial epidural bolus, the potential neurotoxicity of continuous administration of esketamine for labour analgesia should be further investigated.

⇒ The concentration of esketamine in the maternal and fetal plasma which would provide information about the transfer of esketamine from epidural space to maternal circulation and then to fetal circulation as well as the safe threshold of esketamine plasma concentration were not determined.

INTRODUCTION

Lumbar epidural blockade with local anaesthetics (LAs) is considered the gold standard for labour analgesia due to its effective pain relief.[1 2] Nevertheless, epidural labour analgesia may be associated with adverse effects such as prolonged labour, increased instrumental birth rate, reduced ambulatory ability and hypotension, among others.[1 3] These potential adverse effects are related to the dosage (concentration) of LAs administered epidurally. Compared with a high concentration of LAs, less concentrated LAs for epidural labour analgesia were associated with a lower incidence of these adverse effects.[3–5] Thus, the addition of an adjuvant to LA solutions has been a routine practice to allow low-dose techniques, reducing LA-dose-dependent adverse effects. The most commonly used adjuvants are opioids, fentanyl and sufentanil.[1 6] However, neuraxial opioids can produce pruritus, nausea and vomiting.[7]

Therefore, the search for an ideal non-opioid adjuvant for epidural labour analgesia is continuous.

Esketamine [S(+)-isomer], the left-handed optical isomer of racemic ketamine, is a N-methyl-$_D$-aspartate (NMDA) receptor antagonist and exhibits analgesic properties with twofold higher potency in comparison with racemic ketamine.[8] An animal study showed that intrathecal use of preservative-free esketamine did not produce histological alterations of the spinal cord and meninges in a dog model.[9] Clinical studies have demonstrated that epidural esketamine alone or as an adjunctive provided better perioperative analgesia than epidural ropivacaine alone in non-obstetric patients.[10 11] In addition, intravenous esketamine has been administrated in parturients undergoing caesarean delivery, and no obvious adverse effects on neonate or breastfeeding were observed.[12 13] A number of recent studies in human further announced that epidural esketamine co-administered with ropivacaine for labour analgesia could provide excellent analgsia and significantly reduce the incidence of postpartum depression with no obvious side effects.[14 15] However, the optimal dose of esketamine as an adjunct to LAs for epidural labour analgesia has not been investigated so far. Therefore, we designed a prospective, double-blind dose-response study to quantify the LA (ropivacaine)-sparing effect of epidural esketamine at different doses by determining its effect on the median effective concentration (EC_{50}) of ropivacaine, as well as potential maternal and neonatal adverse effects in parturients receiving epidural labour analgesia.

MATERIALS AND METHODS

This study was approved by the Research Ethics Committee of Women's Hospital, Zhejiang University School of Medicine (no. IRB-20210247-R, approved date: September 2, 2021), and the protocol was registered at the Chinese Clinical Trial Registry (identifier: ChiCTR2100054348, PI: XC, registered data: 14 December 2021. URL: https://www.chictr.org.cn/showproj.html?proj=143249) prior to the first participant enrolment. We conducted this study in a single medical centre between 4 January and 15 May 2022. This manuscript adheres to the Consolidated Standards of Reporting Trials guidelines.

Population, randomisation and blinding

After written informed consent was obtained, 150 ASA physical status II subjects who requested labour analgesia were enrolled and informed that esketamine has not been approved by any regulatory body for neuraxial administration and its potential side effects. All participants were at term pregnancy (≥37 weeks of gestational age) with singleton vertex pregnancy in spontaneous labour and cervical dilation of ≤5 cm. Exclusion criteria included allergy to the study drugs, contraindication to neuraxial analgesia, severe obstetric complications and refusal to participate in the study.

Based on a computer-generated randomisation list (Microsoft, Excel), the parturients enrolled were randomly assigned to one of the five groups: Group E0, Group E0.2, Group E0.3, Group E0.4 and Group E0.5. The randomisation sheets were concealed in sequentially numbered opaque envelopes that were opened by one investigator (LX) who was also responsible for preparing the study solution after obtaining written informed consent. The study solutions were prepared in two steps: 1) 50 mg (2 mL) esketamine was diluted with 48 mL saline to achieve a concentration of esketamine at 1 mg/mL; 2) 0 mL, 20 mL, 30 mL, 40 mL or 50 mL of the 1 mg/mL esketamine solusion plus X ml of 0.1% ropivacaine were added with saline to a total volume of 100 mL to achieve the desired concentration of esketamine at 0 mg mL^{-1}, 0.2 mg mL^{-1}, 0.3 mg mL^{-1}, 0.4 mg mL^{-1} or 0.5 mg mL^{-1}, respectively, and the desired concentration of ropivacaine, X=10 mL, 9 mL, 8 mL … could result in a concentration of ropivacaine being 0.1%, 0.09%, 0.08%…. Each medication mixture was labelled with a study serial number only. The investigators (SL and YZ) who performed the study and the paturients were blinded to the group allocation. The study was performed from the study drug administration to postpartum day 1, and the postpartum follow-up was performed by the investigators (SL) twice a day.

Patient and public involvement

No patient or public member was involved in the design and conduct of the study.

Initiation of epidural labour analgesia

All the participants received standard monitoring including ECG, pulse oximeter (SpO_2), and non-invasive blood pressure measurement. A cervical examination was performed at the time of request for labour analgesia. If cervical dilation was less than or equal to 5 cm, the parturient was included in the study. A baseline pain score was obtained before the initiation of epidural analgesia using a 100 mm visual analogue scale (VAS) in which 0 represented no pain and 100 denoted the worst possible pain. Epidural anaesthesia was initiated in the left lateral decubitus position at L2 to L3 interspace estimated by landmarks. Loss of resistance to saline (≤2 mL) was used to identify the epidural space, and a nylon multiorifice catheter was advanced 3–5 cm into the epidural space. A 5 mL and then 15 mL (20 mL in total) of epidural solution containing ropivacaine and esketamine were administered via the epidural catheter. The concentrations of esketamine were 0 mg ml^{-1}, 0.2 mg ml^{-1}, 0.3 mg ml^{-1}, 0.4 mg ml^{-1} and 0.5 mg ml^{-1} for parturients in Group E0, Group E0.2, Group E0.3, Group E0.4 and Group E0.5, respectively, and were kept constant for each group. The concentration of ropivacaine for the first parturient in each group was 0.1% and for the subsequent parturient in each group was determined by the response of the previous parturient to the epidural solution used, according to the up-down sequential allocation method.[16] An effective analgesia was defined as a VAS of ≤10 mm

achieved during uterine contractions within 30 min of epidural injection. An ineffective analgesia was defined as a failure to achieve a VAS of ≤10 mm during uterine contractions within 30 min of epidural injection. A result of effective analgesia directed a decrement of 0.01% and a result of ineffective analgesia directed an increment of 0.01% of ropivacaine concentration for the next parturient in the same group. At 30 min after epidural injection, the parturient with ineffective analgesia was given a rescue bolus of 8 mL 0.3% ropivacaine. Those who were not responsive to the rescue ropivacaine were excluded from the analysis. Further management of these non-responders included replacement of epidural catheter, intrathecal injection of ropivacaine or parenteral analgesic as appropriate. In addition, the subsequent parturient received the same concentration of ropivacaine.

Maintenance of epidural labour analgesia

Programmed intermittent epidural bolus (PIEB) combined with patient-controlled epidural analgesia (PCEA) technique was used for the maintenance of labour analgesia. The PIEB volume was 8 mL administered every hour. The first bolus was administered 30 min after epidural injection. PCEA setting was 8 mL of bolus with a 15 min of lockout time and a 24 ml h^{-1} of maximum volume. The epidural solution for maintenance of analgesia in each group was 0.1% ropivacaine mixed with 2 μg ml^{-1} fentanyl.

Demographic characteristics and outcome assessment

Maternal age, body mass index (BMI), gestational age, maternal blood pressure, cervical dilation and pain VAS score at request for analgesia and duration of labour were recorded. The number of parturients with effective or ineffective analgesia, the analgesia success rate (the percentage of the number of parturients who received effective epidural analgesia out of the number of parturients received epidural analgesia), pain VAS score at 30 min after the epidural injection, satisfaction with the labour/childbirth (assessed on a 100 mm scale from 'very bad' to 'excellent'), labour duration, caesarean section rate, neonatal Apgar score at 1 and 5 min, umbilical artery blood gas pH value after birth and fetal heart rate were also recorded.

Dermatome levels of sensory blockade and motor blockade (were tested on the Bromage scale[17]: 4, full movement of both legs; 3, inability to raise the extended leg, can bend knee; 2, inability to bend knee, can flex ankle; and 1, no movement of both legs) were also assessed every 30 min and recorded.

Sedation level was assessed every 30 min by Ramsay score using a six-point scale (1, restlessness; 2, completely awake, quiet, and cooperative; 3, drowsiness but responding to verbal commands; 4, light sleep but responding to touch or pain; 5, asleep but slowly responding to touch or pain; and 6, deeply asleep and does not respond).[18]

The incidence of adverse events, for instance, hypotension, hypertension, bradycardia, tachycardia and desaturation, was assessed every 30 min by the investigators (SL) from the study drug administration to postpartum day 1 and treated according to medical guidelines. Hypotension was defined as systolic blood pressure below 20% of baseline, hypertension as systolic blood pressure increased above 20% of baseline, bradycardia as heart rate below 60 bpm, tachycardia as heart rate above 100 bpm and desaturation as oxygen saturation below 90%. We also monitored the occurrence of nausea and vomiting, numbness or pain in the limb as well as neurologic and mental signs and symptoms (such as lethargy, diplopia, nystagmus, dizziness, headache, nightmare, hallucination, anxiety and irritability) and managed according to routine practice. Lethargy was defined as a pathological state of sleepiness or deep unresponsiveness and inactivity. Diplopia was defined as a disorder of vision in which two or more images of a single object are seen. Nystagmus was defined as rapid involuntary movements of the eyes.

The primary outcome of the study is the EC_{50} of ropivacaine for labour analgesia. The secondary outcomes were analgesia characteristics, labour duration, caesarean section rate, neonatal Apgar score at 1 and 5 min, umbilical artery blood gas pH value after birth, fetal heart rate and adverse effects.

Statistical analysis

The sample size was calculated based on the results of a previous study[19] that showed the EC_{50} of ropivacaine was 0.089% w/v (95% CI 0.075 to 0.103). Allowing for multiple comparisons to maintain the overall alpha error at the level of 0.05, a conservative threshold alpha error of 0.01 was applied to detect a 50% reduction in the EC_{50} of ropivacaine by esketamine. It was then estimated by the Kruskal–Wallis test of PASS statistical software that a minimum of 16 subjects per group would be required to obtain a power of 90%. In addition, 20 to 40 subjects were needed to provide a stable estimate of the EC_{50} calculated by the modified Dixon up-down method.[20 21] Finally, we applied a sample size of 30 parturients for each group in this study.

The Kolmogorov–Smirnov test was applied to test normality for continuous data. Normally distributed data were presented as mean±SD and analysed among groups using one-way analysis of variance followed by post-hoc pairwise comparisons for significant results. Non-normally distributed data were presented as median and IQR and analysed using the Kruskal–Wallis test with Dunn's tests for post-hoc pairwise comparisons. Categorical data were presented as percentage (%) and analysed using the X^2 test.

The EC_{50} values of ropivacaine were determined by calculating the mean of the midpoints of pairs of ropivacaine concentrations administered in successive patients in which an ineffective analgesia was followed by an effective analgesia or vice versa using the modified up-and-down method.[22 23] The 95% CIs for the EC_{50} values were calculated using the method suggested by Choi.[23] Probit regression analysis (for EC_{50} and EC_{95}) was applied as a

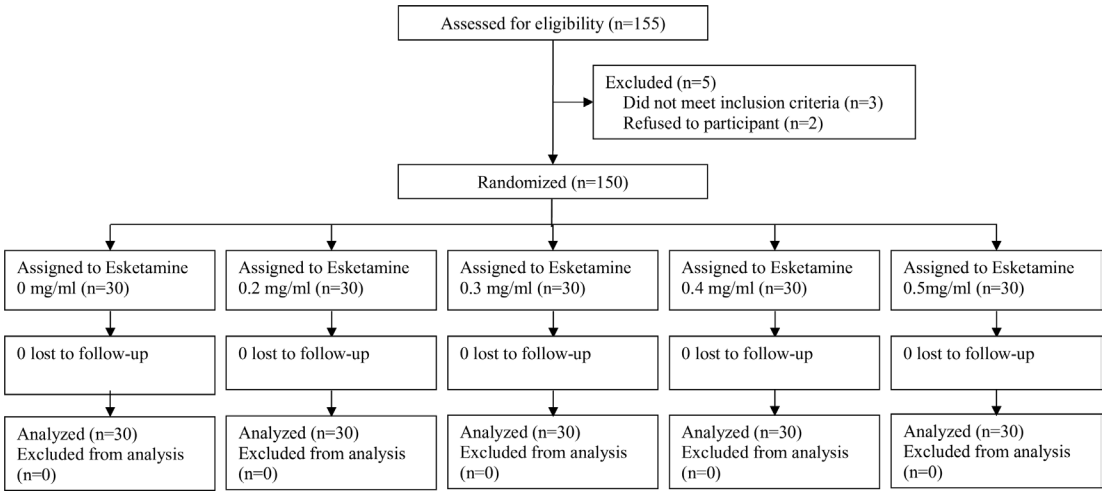

Figure 1 Consolidated Standards of Reporting Trial diagram of patient recruitment.

backup and sensitivity test by analysing tallied numbers of effectiveness and ineffectiveness for each dose category for each group.

IBM SPSS for Windows version 22.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 5.0 (GraphPad Software Inc, San Diego, CA, USA) were used for statistical analysis. *P* value <0.05 was considered statistically significant, with Bonferroni adjustments applied for multiple pairwise comparisons.

RESULTS

One hundred and fifty-five parturients were screened for eligibility, of which three parturients did not meet the inclusion criteria and two parturients declined to participate. A total of 150 parturients were randomised into five groups (n=30 each) and included in the final analysis (figure 1). Baseline demographic and obstetric characteristics were comparable between groups (table 1).

The sequences of effective and ineffective labour analgesia are presented in figure 2. The calculated EC_{50} values for epidural ropivacaine mixed with different concentrations of esketamine determined by up-down sequential allocation method are presented in table 2. There were significant differences in the EC_{50} for ropivacaine among groups using Kruskal–Wallis test (p<0.0001) with a significant linear trend (p<0.0001). Dunn post test for multiple comparisons showed a significant reduction in the EC_{50} for ropivacaine in the E0.3 (p=0.002), E0.4 (p<0.0001) and E0.5 (p<0.0001)] groups, but no reduction in the E0.2 group (p=0.117), compared with the E0 group. Moreover, the EC_{50} did not differ significantly among groups E0.3, E0.4 and E0.5 (p>0.99).

Probit regression analysis also showed that the EC_{50} values of ropivacaine were lower in patients given 0.3 mg mL^{-1} (0.049% (95% CI 0.040 to 0.057)), 0.4 mg mL^{-1} (0.044% (95% CI 0.036 to 0.053)) and 0.5 mg ml^{-1}

Table 1 Patient characteristics

	Esketamine 0mg ml^{-1} (n=30)	Esketamine 0.2 mg ml^{-1} (n=30)	Esketamine 0.3 mg ml^{-1} (n=30)	Esketamine 0.4 mg ml^{-1} (n=30)	Esketamine 0.5 mg ml^{-1} (n=30)
Age (years)	29.7±3.6	29.5±3.3	31.0±4.1	30.3±3.2	30.5±3.5
Height (cm)	161.1±4.7	162.1±6.3	162.2±4.7	162.5±4.7	161.9±4.7
Weight (kg)	70.7±8.5	68.6±8.3	68.4±10.0	67.3±7.8	67.8±6.0
Gestational age (weeks)	39.4 (38.8, 40.0)	39.4 (38.9, 40.0)	39.6 (39.3, 40.1)	39.4 (38.8, 40.0)	39.0 (38.4, 39.4)
Pain visual analogue scale score (0–100 mm)*	82 (71, 92)	89 (80, 100)	83 (75, 100)	90 (78,100)	85 (80, 90)
Cervical dilation (cm)*	3.0 (2.0, 3.0)	3.0 (3.0, 3.0)	3.0 (2.0, 3.0)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)
Number of gravidities	1 (1, 2)	1 (1, 2)	1 (1, 1)	1 (1, 2)	1 (1, 2)
Number of parturitions	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Oxytocin	12 (40.0)	14 (46.7)	13 (43.3)	15 (50.0)	12 (40.0)

Data are presented as mean±SD or median (IQR).
*Pain visual analogue scale score and cervical dilation were assessed at the time of request for analgesia.

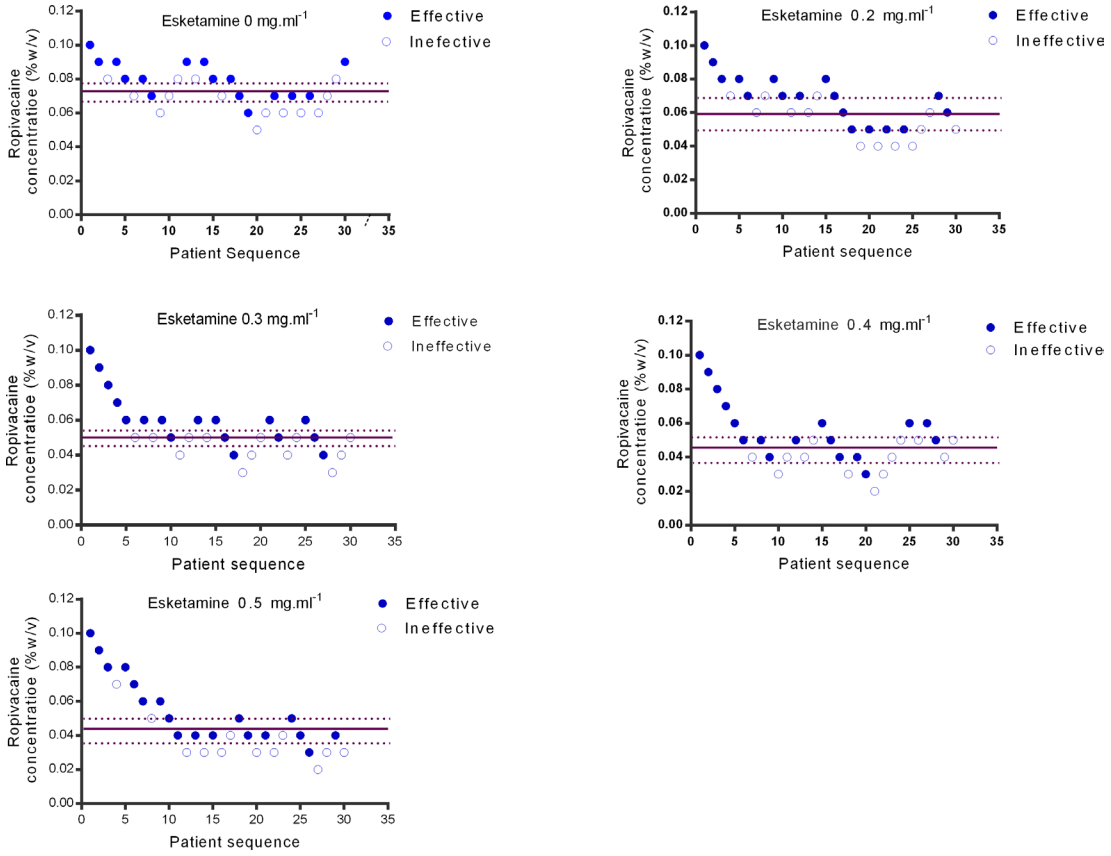

Figure 2 Median effective concentration (EC_{50}) of epidural ropivacaine and with addition of esketamine 0 mg ml^{-1}, 0.2 mg ml^{-1}, 0.3 mg ml^{-1}, 0.4 mg ml^{-1} and 0.5 mg ml^{-1} as determined by the up-down sequential allocation technique. The solid lines represent the EC_{50}, and the dashed lines represent 95% CIs. The testing interval was 0.01% w/v.

(0.040% (95% CI 0.031 to 0.048)) epidural esketamine when compared with those given 0 mg ml^{-1} (0.073% (95% CI 0.0641 to 0.081)) or 0.2 mg ml^{-1} (0.059% (95% CI 0.050 to 0.067)) epidural esketamine (p<0.001). The EC_{95} of ropivacaine was lower in patients given 0.3 mg ml^{-1} (0.074% (95% CI 0.065 to 0.090)), 0.4 mg ml^{-1} (0.070% (95% CI 0.060 to 0.086)) and 0.5 mg ml^{-1} (0.065% (95% CI 0.056 to 0.081)) epidural esketamine when compared with those given 0 mg ml^{-1} (0.098% (95% CI 0.089 to 0.114)) or 0.2 mg ml^{-1} (0.084% (95% CI 0.075 to 0.100)) epidural esketamine (p<0.001). Dose response curves derived from probit regression analysis are shown in online supplemental figure 1.

The consumptions of ropivacaine were significantly lower in groups E0.3, E0.4 and E0.5 compared with the group E0 and E0.2, and no differences among the groups E0.3, E0.4 and E0.5. The Ramsay sedation scores in group E0.5 were higher than that in all other groups (all p<0.05), and no differences were found among the other groups (table 3).

Table 2 Median effective concentration of ropivacaine and effect of esketamine

Group (n=30)	EC_{50} of ropivacaine (95% CI, % w/v)	Dunn p value* (adjusted)	EC_{50} of ropivacaine (95% CI, % w/v)	EC_{95} of ropivacaine (95% CI, % w/v)
Ropivacaine–esketamine 0 mg ml^{-1}	0.073 (0.068, 0.078)		0.073 (0.0641, 0.081)	0.098 (0.089, 0.114)
Ropivacaine–esketamine 0.2 mg ml^{-1}	0.059 (0.052, 0.065)	0.117	0.059 (0.050, 0.067)	0.084 (0.075, 0.100)
Ropivacaine–esketamine 0.3 mg ml^{-1}	0.050 (0.046, 0.055)	0.002	0.049 (0.040, 0.057)	0.074 (0.065, 0.090)
Ropivacaine–esketamine 0.4 mg ml^{-1}	0.044 (0.038, 0.050)	<0.0001	0.044 (0.036, 0.053)	0.070 (0.060, 0.086)
Ropivacaine–esketamine 0.5 mg ml^{-1}	0.043 (0.035, 0.050)†	<0.0001	0.040 (0.031, 0.048)	0.065 (0.056, 0.081)

Kruskal–Wallis (among all groups) test, p<0.0001.
*p value compared with ropivacaine-esketamine 0 mg ml^{-1}.
†p=0.020 compared with ropivacaine-esketamine 0.2 mg ml^{-1}.
EC_{50}, median effective concentration.

Table 3 Analgesia outcomes, obstetric outcomes and side effects

	Esketamine 0 mg ml^{-1} (n=30)	Esketamine 0.2 mg ml^{-1} (n=30)	Esketamine 0.3 mg ml^{-1} (n=30)	Esketamine 0.4 mg ml^{-1} (n=30)	Esketamine 0.5 mg ml^{-1} (n=30)	p value
Sensory level at 30 min after the epidural injection	T10 (T8, T10)	T9 (T6, T10)	T10 (T8, T10)	T10 (T8, T10)	T9 (T8, T10)	0.971
Bromage score at 30 min after the epidural injection	0	0	0	0	0	–
Ropivacaine consumption (mg h^{-1})	12.0 (9.5, 13.9)	10.5 (7.9, 12.5)	9.5 (7.4, 11.0)*	9.4 (7.1, 11.3)*	9.0 (7.1, 11.0)*	0.002
Number of parturients with effective analgesia	16	17	17	18	18	0.995
Number of parturients with ineffective analgesia	14	13	13	12	12	0.995
Analgesia success rate (%)	53.3	56.7	56.7	60.0	60.0	
Pain visual analogue scale score at 30 min after the epidural injection (0–100 mm)	10 (7, 45)	8 (3, 45)	9 (7, 41)	9 (7, 39)	9.0 (8, 38)	0.880
Satisfaction with labour/childbirth at 1 hour after delivery (%)	98 (87, 100)	98 (86, 100)	98 (89, 100)	96 (89, 99)	97 (86, 100)	0.960
Labour duration (min)						
First stage	560 (407, 751)	450 (294, 556)	420 (243, 867)	419 (280, 611)	510 (364, 690)	0.077
Second stage	54 (33, 92)	51 (31, 102)	64 (47, 121)	41 (30, 57)	59 (37, 104)	0.157
Caesarean delivery (n, %)	5 (16.7)	2 (6.7)	3 (10.0)	2 (6.7)	2 (6.7)	0.728
Hypotension (n, %)	1 (3.3)	0 (0.0)	1 (3.3)	0 (0.0)	3 (10.0)	0.274
Ramsay score	2 (2, 2)	2 (2, 2)	2 (2, 2)	2 (2, 2)	2 (2, 2)*†‡§	<0.001
Desaturation¶ (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Numbness or pain in the limb (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Dizziness (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.0)	4 (13.3)*†‡	0.013
Vertigo (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Hallucination (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Diplopia (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Nightmare (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Nystagmus (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–

Continued

Table 3 Continued

	Esketamine 0 mg ml^{-1} (n=30)	Esketamine 0.2 mg ml^{-1} (n=30)	Esketamine 0.3 mg ml^{-1} (n=30)	Esketamine 0.4 mg ml^{-1} (n=30)	Esketamine 0.5 mg ml^{-1} (n=30)	p value
Irritability (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Headache (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Vertigo (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Fetal bradycardia (n, %)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	>0.999
Umbilical artery PH	7.34±0.07	7.35±0.10	7.32±0.04	7.33±0.04	7.36±0.09	0.306
Apgar score at 1 min	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	0.462
Apgar score at 5 min	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	10 (10, 10)	>0.999

Data are presented as number (%), mean±SD or median (IQR).
*p<0.005, compared with esketamine 0 mg·mL^{-1} after Bonferroni correction.
†p<0.005, compared with esketamine 0.2 mg·mL^{-1} after Bonferroni correction.
‡p<0.005, compared with esketamine 0.3 mg·mL^{-1} after Bonferroni correction.
§p<0.005, compared with esketamine 0.4 mg·mL^{-1} after Bonferroni correction.
¶Desaturation was defined as oxygen saturation below 90%.

During the peripartum period, no differences in sensory blockade level, Bromage score, parturients satisfaction, labour duration, percent of caesarean delivery, maternal adverse effects (hypotension, respiratory depression) and fetal outcomes (umbilical artery PH, Apgar score) were found among groups (all p>0.05) (table 3). Patients given epidural esketamine 0.5 mg·mL^{-1} developed more dizziness than patients given epidural esketamine 0 mg·mL^{-1} to 0.4 mg·mL^{-1} (p<0.001). The incidences of numbness or pain in the limb and other neurological or mental symptoms did not differ among five groups (table 3).

DISCUSSION

In this prospective, double-blind, randomised study, we found that the addition of epidural esketamine produced a dose-dependent reduction in EC_{50} values of epidural ropivacaine for labour analgesia, showing a ropivacaine-sparing effect by the epidural esketamine. To our best knowledge, it is the first study to investigate epidural esketamine as an adjuvant to ropivacaine in epidural labour analgesia and its effect on the minimum local anaesthetic concentration (MLAC) of ropivacaine.

The MLAC, defined as EC_{50} in a 20 ml volume, has been validated to be a clinical study model for estimating the LA-sparing potential of epidural adjuncts during labour analgesia.[19 24] The present study revealed that a significant reduction in the EC_{50} of ropivacaine for epidural labour analgesia was achieved by the addition of esketamine at 0.3 mg ml^{-1}, 0.4 mg ml^{-1} or 0.5 mg ml^{-1} administered epidurally, and no reductions were achieved with 0.2 mg ml^{-1} of esketamine, suggesting that greater than 0.2 mg ml^{-1} of esketamine is required to produce a significant ropivacaine-sparing effect. Moreover, the addition of esketamine with 0.3 mg ml^{-1}, 0.4 mg ml^{-1} or 0.5 mg ml^{-1} resulted in a similar reduction of the EC_{50} of ropivacaine (similar sparing-effect to ropivacaine), suggesting the concentration of esketamine exceed 0.3 mg ml^{-1} is not necessary for the initiation of labour analgesia.

Esketamine has been widely used in clinical practice for over 20 years.[11–13 25–28] Esketamine possesses two to three-fold greater analgesic potency of the racemic ketamine and now available as a preservative-free drug that is recommended for supplemental analgesia during neuraxial administration. Previous studies suggested that addition of epidural esketamine to LAs (ropivacaine or bupivacaine) during surgery could provide better postoperative analgesia with longer duration than epidural ropivacaine or bupivacaine alone in non-obstetric patients.[10 28] Unlugenc *et al* found that addition of intrathecal esketamine to bupivacaine led to rapid onset of both sensory and motor blockade and enhanced the segmental spread of spinal block in patients undergoing caesarean section.[27] The present study also demonstrated the additive effect of epidural esketamine to ropivacaine by the fact that epidural esketamine significantly reduced the requirements of epidural ropivacaine (both concentration and dose) for labour analgesia.

The mechanisms of epidural esketamine analgesia remain to be elucidated. Martindale *et al*[28] compared the analgesic efficacy of esketamine administered caudally or intravenously for postoperative pain control and found that caudal esketamine provided better analgesia than intravenous esketamine, suggesting that the principal analgesic site of caudal esketamine is neuraxial rather than systemic. Esketamine is a non-competitive antagonist of NMDA receptor which is found throughout the

central nervous system including the lumbar spinal cord and plays an important role in nociceptive processing.[29 30] Esketamine is highly lipid soluble and easily crosses the dura into the subarachnoid space to exert its analgesic effect. Another possible mechanism of analgesic effect may result from esketamine agonist activity at mu-opioid receptors and interaction with several ion channels.[29] In addition, the additive (or synergistic) analgesic effects produced by epidural esketamine might play a role since esketamine administered epidurally was detected rapidly in systemic circulation in a previous study.[10] The mechanisms of additive (of synergistic) analgesia of epidural esketamine and ropivacaine also need to be investigated.

The use of epidural esketamine may elicit concern about potential neurotoxicity. A study with a single dose of intrathecal injection of preservative-free esketamine with a concentration range of 6 to 15 mg ml^{-1} in dogs found no alterations in the ultrastructural neuro-histopathology of the spinal cord and meninges.[9] Another animal study also indicated that repeated epidural injection of preservative-free esketamine over 10 days at concentration of 50 mg ml^{-1}, which is much higher than that used in clinical settings (0.2 to 0.5 mg ml^{-1}), did not produce ultrastructural alterations in canine meninges and alteration in neurological behaviour.[31] Several clinical studies with epidural or intrathecal use of preservative-free esketamine for perioperative pain management have not shown obvious signs of neuraxial injury in obstetric patients, non-obstetric patients or children, though these studies did not have neurotoxicity of epidural esketamine as the primary outcome.[10 11 13 27 28 32] The current study also did not find any signs of neuronal damage in the parturients. However, given that esketamine was used only as an initial epidural bolus, the potential neurotoxicity of continuous administration of esketamine for labour analgesia should be further investigated in a large robust study.

Another major concern is potential maternal and neonatal adverse effects of epidural esketamine. A previous study[12] using intravenous esketamine 0.15 mg kg^{-1} administered before caesarean delivery showed favourable effect on maternal and neonatal outcomes, except more parturients had dizziness in the esketamine group. Consistent with a previous study using neuraxial esketamine,[27] the present study did not observe any psychological events or respiratory depression in all groups during the study period. However, the parturients in group E0.5 presented with higher Ramsay sedation scores than those in the groups with 0.4 mg ml^{-1} or less concentrations of esketamine, suggesting that 0.4 mg ml^{-1} or less of epidural esketamine would be safer in terms of maternal adverse effects. In addition, no newborns in the present study manifested compromised outcomes such as low Apgar scores, which are also in agreement with the findings reported previously.[12] A recent review indicated that esketamine use during caesarean section delivery may not affect lactation and breastfeeding.[33]

There are several limitations in our study. First, we did not measure the concentration of esketamine in the maternal and fetal plasma, which would provide information about the transfer of esketamine from epidural space to maternal circulation, then to fetal circulation, also about the safe threshold of esketamine plasma concentration. Further studies will address this issue. Second, our sample size determined according to the up-down method was small. Future studies with a large sample size are required to determine the neurotoxicity and validate the safety of epidural esketamine for labour analgesia. Third, we did not compare the analgesic efficacy and adverse effects between esketamine and fentanyl (or sufentanil) administered epidurally as an adjuvant to LAs for labour analgesia. Further studies on this topic are warranted. Fourth, in our study, supplemental esketamine was used only as an initial epidural bolus, the potential neurotoxicity of continuous administration of esketamine for labour analgesia should be further investigated in a large robust study. Fifth, as noted before, the study design did not allow our investigators to draw a conclusion about the optimal dose of esketamine when administered with a clinically relevant dose of ropivacaine (ED95).

CONCLUSIONS

The addition of epidural esketamine at doses from 0.3 to 0.5 mg mL^{-1} for the initiation of labour analgesia significantly reduced EC_{50} of ropivacaine and produced a dose-dependent sparing effect to ropivacaine for epidural labour analgesia. However, further large-scale studies on the safety and efficacy of esketamine used for maintanence of epidural labour analgesia are warranted.

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