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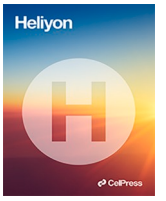

Research article

Epidural dexmedetomidine or esketamine versus fentanyl to decrease ropivacaine use for labor analgesia: A randomized non-inferiority study

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ABSTRACT

Background: Epidural nonopioid adjuvants also reduce local anesthetic use. We aimed to test the hypothesis that, compared with the present standard fentanyl, the hourly consumption of local anesthetic was at least as good when dexmedetomidine or esketamine was combined with local anesthetic for patient-controlled epidural analgesia (PCEA).

Methods: A total of 120 laboring nulliparous subjects requiring labor analgesia were recruited for the final statistical analysis. Subjects were randomized to receive 0.075 % ropivacaine added with one of three equivalent adjuvants: 0.4 μg/mL fentanyl, 0.4 μg/mL dexmedetomidine, or 1.0 mg/mL esketamine. The primary outcome was hourly ropivacaine consumption. Compared with the fentanyl group, a 20 % difference in hourly local anesthetic consumption between the dexmedetomidine and esketamine groups was considered a clinical difference (non-inferiority margin).

Results: The hourly ropivacaine consumption of the fentanyl group was 12.4 (95 % confidence interval CI 11.2 to 13.6) ml/h, so the prespecified non-inferiority limit was 2.5 ml/h. The hourly ropivacaine consumption of the fentanyl group was not inferior to that of the dexmedetomidine group (12.4 ml/h vs. 11.9 ml/h, risk difference, 0.5; 95 % confidence interval CI, −1.0 to 2.0, meeting criteria for non-inferiority). However, the hourly ropivacaine consumption of the esketamine group was 14.3 ml/h, and that of the fentanyl group was 12.4 ml/h (risk difference, 1.9, 95 % CI, 0.2 to 3.6), failing to confirm non-inferiority with a non-inferiority margin of 20 %. The incidence of pruritus was highest in the fentanyl group, whereas the occurrence of mild dizziness was highest in the esketamine group.

Conclusions: In setting of the conditions of this study, epidural dexmedetomidine was non-inferior compared with epidural fentanyl in combination with ropivacaine for PCEA during labor.

Abbreviations: NRS pain scores, numerical rating scale pain scores; CI, confidence interval; ASA, American Society of Anesthesiologists; PCEA, patient controlled epidural analgesia; ANOVA, analysis of variance; CRNA, certified registered nurse anesthesia; CONSORT Flow Diagram, Consolidated Standards of Reporting Trials Flow Diagram.

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Meanwhile, we failed to establish the non-inferiority of epidural esketamine compared with epidural fentanyl in combination with ropivacaine for labor analgesia.

1. Introduction

Studies suggest that ultra-low concentrations and larger volumes of local anesthetics combined with different adjuvants would result in a local anesthetic-sparing effect, produce more effective labor analgesia, maintain the maternal ability to void and ambulate, and reduce the occurrence of side effects [1–4]. The addition of traditional adjuvant fentanyl to local anesthetics can reduce the consumption of local anesthetics without affecting the quality of analgesia [5]. However, epidural administration of nonopioid adjuvants (e.g., dexmedetomidine or esketamine) can also produce similar satisfactory labor analgesia [6,7].

The optimum concentrations of different adjuvants with 0.075 % ropivacaine for PCEA were fentanyl 0.4 μg/mL, dexmedetomidine 0.4 μg/mL, and esketamine 1.0 mg/mL, respectively [6–8]. A 20 % difference in hourly local anesthetic consumption has been reported as a clinical difference (non-inferiority margin) [9]. To date, no trial has been performed to show the non-inferiority of the hourly consumption of local anesthetics using these equivalent adjuncts in combination with local anesthetics for PCEA.

Therefore, based on this information, we conducted this randomized, non-inferiority trial to test the hypothesis that the hourly consumption of ropivacaine is at least as good when dexmedetomidine or esketamine is combined with local anesthetic for PCEA as compared with the present standard fentanyl.

2. Materials and methods

2.1. Design and study subjects

The randomized, non-inferiority trial was approved by the Ethical Committee of Affiliated Xiaoshan Hospital, Hangzhou Normal University (Hangzhou, China) in February 2022 (approval number: KL2022015), and the protocol was registered in the Chinese Clinical Trial Registry on August 1, 2022 (https://www.chictr.org.cn/bin/project/edit?pid = 159765; ChiCTR2200062309). All patients provided informed consent to participate in the study. We confirm our study has complied the CONSORT guidelines. Primiparas with singleton pregnancies were enrolled if they were 18 years or older, American Society of Anesthesiologists physical status (ASA) II, height greater than or equal to 150 cm, and weight less than or equal to 100 kg. The exclusion criteria were allergy to fentanyl, dexmedetomidine or esketamine, contraindication to neuraxial analgesia, presence of maternal bradycardia, and declined to participate in the study. Ultimately, 120 subjects were recruited for the final statistical analysis between August 3, 2022 and June 8, 2023.

2.2. Study protocol

Subjects were randomly assigned to one of the three study groups in a 1:1:1 ratio using a computer-generated code sequence hidden in opaque sealed envelopes. All participants in this study were blinded to the group allocation and study solution. A certified registered nurse anesthesia (CRNA) not involved in the subsequent trial prepared the study solution. Subjects were randomized to receive 0.075 % ropivacaine added with one of three adjuvants: 0.4 μg/mL fentanyl, 0.4 μg/mL dexmedetomidine, or 1.0 mg/mL esketamine.

Pain was assessed using the numerical rating scale (NRS) (scale 0 = no pain, 10 = the worst pain) before epidural analgesia. Analgesia was performed in the left lateral position at the L2/3 or L3/4 vertebral interspace using the loss-of-resistance-to-air technique with an 18G Tuohy needle. An epidural catheter was inserted into the epidural space 3–5 cm. The epidural catheter was connected to the PCEA infusion pump (REHN11; Jiangsu Renxian Medical Technology Co., Ltd.) with the following parameters: loading dose of 15 mL (the first dose of epidural injection), background administration rate of 5 mL, bolus of 10 mL when NRS pain score was >3 with 20 min lockout interval, and maximum dose of 30 mL per hour. Adequate analgesia was defined as an NRS pain score ≤3 30 min after epidural loading dose administration. If analgesia was inadequate, 10 ml of 1 % lidocaine was injected epidurally and repeated for 15 min as required. The subject was withdrawn from this study, and the next subject was scheduled to receive the same adjuvant. When the NRS pain score was still >3 after the second application of lidocaine, the epidural catheter was considered misplaced and repositioned.

Pain score, bilateral level of sensory block to pinprick, degree of motor block, blood pressure, heart rate, pulse oximetry, and fetal heart rate were recorded every 5 min for 30 min after epidural loading dose administration, and then every 1 h until delivery.

The primary outcome was hourly ropivacaine consumption (the total amount of ropivacaine administered by the pump divided by the time from pump initiation to fetal delivery). Secondary outcomes included duration of stage of labor, Apgar scores and side effects (pruritus, nausea and vomiting, respiratory depression defined as maternal SpO2 < 95 %, excessive sedation defined as Ramsay Sedation Scale value > 4, bradycardia defined as heart rate <60 bpm, hypotension defined as a 20 % reduction or more from baseline and maternal fever defined as maternal temperature ≥38 °C). Dizziness was evaluated using dizziness grading criteria (severe: grade 4 to 5; moderate: grade 2 to 3; mild: grade 1): 5 = Patient was unable to take care of herself after dizziness episodes and needed help from others; 4 = Patient was unable to take care of herself after dizziness attack; 3 = Patient can take care of most of her daily life after dizziness attack; 2 = Patient was forced to stop daily life when dizziness occurred and recovered completely soon after dizziness attack; 1 = Daily life was not affected during and after the dizziness attack.

2.3. Statistical analysis

The primary outcome was hourly ropivacaine consumption per group. The final analysis of our pre-experiment showed a mean hourly ropivacaine use of 10.5 ± 3.1 ml/h with the addition of epidural fentanyl. Based on these new data and previous studies [9,10], a sample of 31 subjects per group would be required to determine a 20 % clinical difference (non-inferiority margin) in ropivacaine consumption per hour between any group ($1-\beta = 0.90$; $\alpha = 0.05$). The null hypothesis was that the consumption of ropivacaine per hour in the dexmedetomidine and esketamine groups was no more than 20 % higher than that in the fentanyl group. Forty subjects were recruited to account for drop-outs. The sample size was calculated using non-inferiority tests for two means (ratios) of PASS 11 (NSCC, LCC, Kaysville, UT, USA).

Data were evaluated for normal distribution using the Shapiro-Wilk test and shown as mean (±SD) or median (with quartiles) and analyzed using one-way ANOVA or Mann-Whitney *U* test, as appropriate. The chi-square test or Fisher's exact test was used to compare frequency data. Statistical significance was set than 0.05. All analyses were performed using SPSS software (version 25.0) for Windows (IBM Corp, Armonk, NY, USA) and R software (version 4.2.2).

3. Results

One hundred and seventy-eight subjects were invited to participate in the study, and data from 120 subjects (40 in each group), were included in the final analysis (Fig. 1). Demographic data are shown in Table 1. There were no statistically significant differences in age, height, weight, gestational age, cervical dilation, or NRS before epidural administration among the three groups.

The analgesic characteristics and labor outcomes are summarized in Table 2. Sensory block level, Bromage score >0, onset of analgesia, PCEA analgesia duration, duration of second stage, spontaneous labor, induced labor, cesarean delivery rate, and Apgar score 1 min and 5 min did not differ among the three study groups. Compared to the fentanyl and dexmedetomidine groups, hourly ropivacaine consumption, PCEA requests, and PCEA successful boluses were significantly increased in the esketamine group.

The mean hourly ropivacaine consumption of subjects in the fentanyl group with 95 % CI was 12.4 (11.2–13.6) ml/h, and that in the dexmedetomidine and esketamine groups was 11.9 (10.9–13.0), and 14.3 (13.4–15.2) ml/h, respectively (Fig. 2). According to the value of the mean ropivacaine consumption per hour in the fentanyl group in this study, the non-inferiority margin (20 % clinical difference) was determined to be 2.5 ml/h. The hourly ropivacaine consumption of the fentanyl group was not inferior to that of the dexmedetomidine group (12.4 ml/h vs. 11.9 ml/h, risk difference, 0.5; 95 % confidence interval CI, −1.0 to 2.0, meeting criteria for

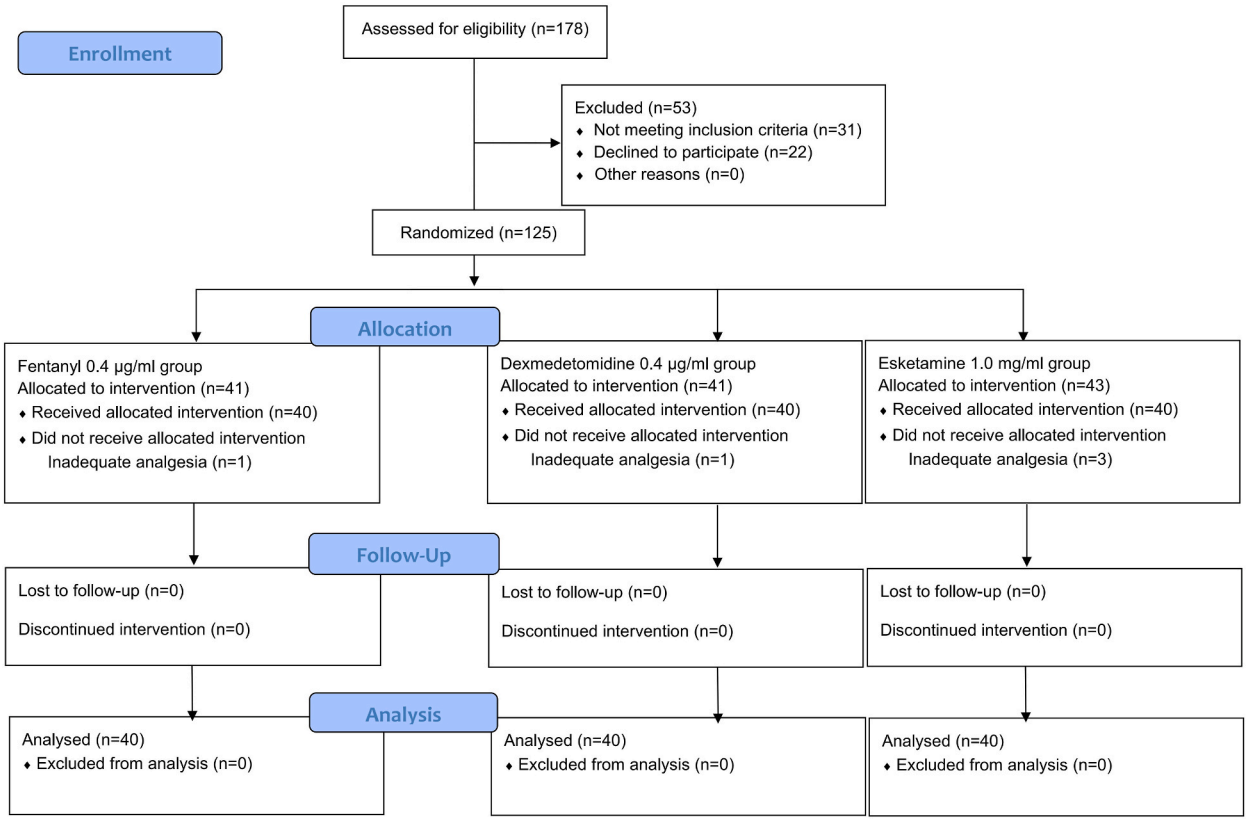

Fig. 1. CONSORT flow diagram.

Table 1
Demographic data.

	Fentanyl, 0.4 μg/ml (n = 40)	Dexmedetomidine, 0.4 μg/ml (n = 40)	Esketamine, 1.0 mg/ml (n = 40)	*P* value
Age (years)	26.9 ± 3.2	25.8 ± 3.6	27.4 ± 2.3	0.10
Height (cm)	161.0 ± 4.9	162.3 ± 5.0	162.0 ± 4.5	0.55
Weight (kg)	68.4 ± 8.3	69.5 ± 8.4	68.7 ± 8.5	0.64
Gestational age (weeks)	39.1 ± 0.9	39.0 ± 0.7	39.1 ± 0.9	0.74
Cervical dilation (cm)	2.6 ± 0.6	2.5 ± 0.6	2.7 ± 0.5	0.70
NRS before epidural	6 (5–7)	6 (5–7)	6 (5–7)	0.63

Data are presented as the mean ± standard deviation (SD), or median (interquartile range).

Table 2
Analgesia characteristics and labor outcomes.

	Fentanyl, 0.4 μg/ml (n = 40)	Dexmedetomidine, 0.4 μg/ml (n = 40)	Esketamine, 1.0 mg/ml (n = 40)	*P* value
Hourly ropivacaine consumption (ml/h)[a]	12.4 ± 3.8	11.9 ± 3.3	14.3 ± 2.9	<0.01
PCEA requests (n)[b]	4 (2–7)	4 (2–6)	7 (4–10)	<0.01
PCEA successful boluses (n)[c]	3 (2–5)	3 (2–4)	6 (4–7)	<0.01
Sensory block level (pinprick)	T10 (9–10)	T10 (8–10)	T9 (8–10)	0.26
Bromage score >0	0 (0 %)	0 (0 %)	0 (0 %)	>0.99
Onset of analgesia (minutes)	15.8 ± 4.2	14.2 ± 3.6	15.5 ± 4.5	0.10
PCEA analgesia duration (minutes)	411.5 ± 181.6	442.9 ± 172.4	428.7 ± 158.2	0.70
Spontaneous labor	28 (70.0 %)	30 (75.0 %)	32 (80.0 %)	0.59
Induced labor	7 (17.5 %)	7 (17.5 %)	2 (5.0 %)	0.17
Cesarean delivery rate	5 (12.5 %) (n = 35)	3 (7.5 %) (n = 37)	6 (15.0 %) (n = 34)	0.57
Duration of first stage (minutes)	481.5 ± 194.6	567.1 ± 270.0	566.2 ± 142.2	0.06
Duration of second stage (minutes)	70.7 ± 33.4	68.6 ± 35.4	65.0 ± 37.4	0.62
Apgar score, 1 min	10 (10–10)	10 (10–10)	10 (10–10)	0.37
Apgar score, 5 min	10 (10–10)	10 (10–10)	10 (10–10)	0.37

Data are presented as the mean ± standard deviation (SD), median (interquartile range), or number (%).
[a] Group Esketamine differed from Group Fentanyl (P = 0.001) and Group Dexmedetomidine (P < 0.001).
[b] Group Esketamine differed from Group Fentanyl (P = 0.004) and Group Dexmedetomidine (P < 0.001).
[c] Group Esketamine differed from Group Fentanyl (P < 0.001) and Group Dexmedetomidine (P < 0.001).

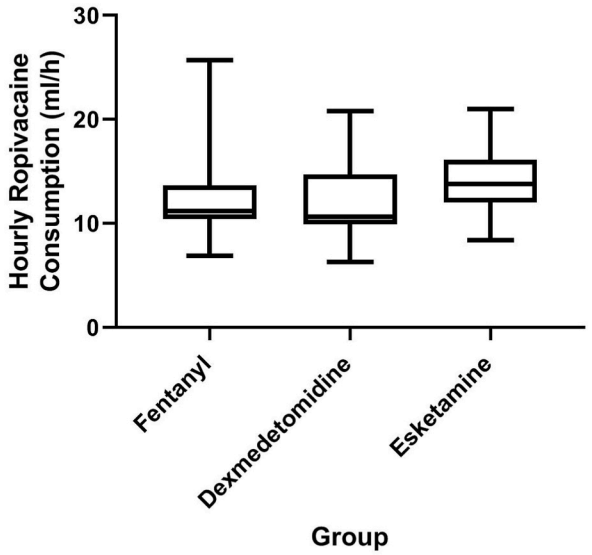

Fig. 2. Mean hourly ropivacaine consumption between groups. The mean hourly ropivacaine consumption of subjects in fentanyl group was 12.4 ± 3.8 ml/h, and in dexmedetomidine and esketamine groups was 11.9 ± 3.3, and 14.3 ± 2.9 ml/h, respectively.

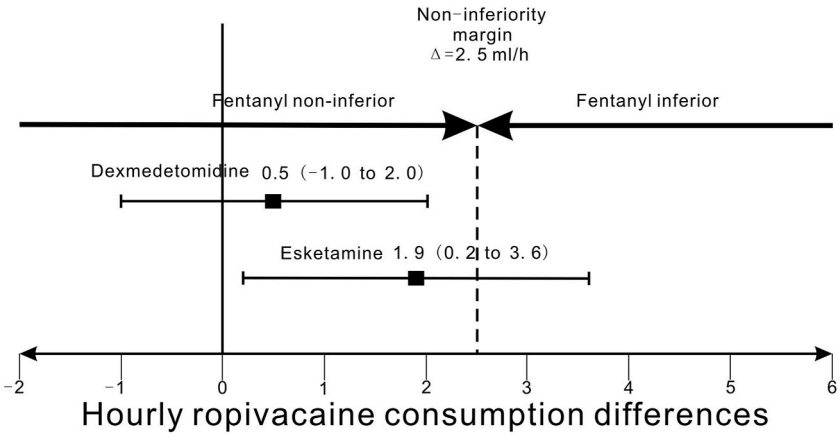

Fig. 3. Non-inferiority diagram of mean hourly ropivacaine consumption differences in the dexmedetomidine group and fentanyl group, or the esketamine group and fentanyl group. Error bars indicate the 95 % CIs of the difference between groups. Δ, non-inferiority margin 2.5 ml/h.

non-inferiority). However, the hourly ropivacaine consumption of the esketamine group was 14.3 ml/h, and that of the fentanyl group was 12.4 ml/h (risk difference, 1.9, 95 % CI, 0.2 to 3.6), failing to confirm non-inferiority with a non-inferiority margin of 20 % (Fig. 3).

The incidence of side effects was comparable among the groups with the exception of pruritus, which was higher in the fentanyl group than in the other two groups. Additionally, the occurrence of mild dizziness was significantly higher in the esketamine group than in the fentanyl and dexmedetomidine groups (Table 3).

4. Discussion

Based on our definition of minimum clinical difference in hourly ropivacaine requirement, we confirmed our hypothesis that dexmedetomidine in combination with ropivacaine was non-inferiority to fentanyl in combination with ropivacaine for PCEA for labor. The incidence of pruritus was lower with epidural administration of dexmedetomidine than with epidural fentanyl. In contrast, we failed to establish the non-inferiority of epidural esketamine compared with epidural fentanyl as a solo adjuvant to epidural ropivacaine for labor analgesia. The incidence of mild dizziness was significantly higher with epidural esketamine than with fentanyl.

Epidural opioids are considered the most classical adjuvants, with the advantage of rapid onset and satisfactory labor analgesia [1,11]. However, it also causes pruritus, decreased ventilation, and fetal heart rate abnormalities [5,12]. Therefore, there has been an interest in an ideal adjuvant that avoids these side effects without compromising the analgesic effect. We conducted this non-inferiority trial to compare the efficacy of potentially ideal adjuvants (e.g., dexmedetomidine or esketamine) with the current standard of fentanyl in reducing epidural local anesthetic consumption.

The choice of fentanyl 0.4 μg/mL, suggested by a previous study using an equipotent local anesthetic for PCEA during labor [8]. In addition, our prior studies found the optimum concentrations of different adjuvants with 0.075 % ropivacaine for PCEA were dexmedetomidine 0.4 μg/mL, and esketamine 1.0 mg/mL, respectively [6,7]. Our study is the first to compare the effect of the use of equipotent adjuvants on the hourly local anesthetic requirement. With a prior definition of 20 % difference in hourly local anesthetic consumption compared with epidural fentanyl, our study is designed to focus on clinical as opposed to statistical significance [9,10].

Our results are consistent with the findings of numerous studies using different recipes of opiods or dexmedetomidine combined with local anesthetics [13–15]. We found that hourly consumption of local anesthetic was at least as good when epidural dexmedetomidine was used in combination with ropivacaine for PCEA compared with the epidural fentanyl group. Moreover, the occurrence of pruritus was lower in the dexmedetomidine group. In our clinical center, dexmedetomidine has been used as an epidural adjuvant for labor analgesia for more than one year, with approximately 5000 cases, and no significant maternal or neonatal side effects have been found. Therefore, dexmedetomidine may be an ideal alternative to opioid adjuvant, which needs to be proven by multi-center studies with larger sample sizes.

Whether epidural esketamine bolus alone or in combination with other adjuvants produces effective epidural analgesia is controversial [7,16–19]. We could not demonstrate the non-inferiority of epidural esketamine as an adjuvant to ropivacaine compared to epidural fentanyl for labor analgesia. However, we determined that epidural esketamine promoted less effective analgesia and a higher incidence of mild dizziness than fentanyl [7]. Therefore, we do not recommend esketamine as a single adjuvant for epidural analgesia.

The configuration method of ultra-low concentration and larger volume of local anesthetics has been advocated by numerous attending anesthesiologists, with the advantages of a local anesthetic-sparing effect, more effective labor analgesia, maintenance of the maternal ability to void and ambulate, and reduction of the occurrence of side effects [3,4,20–22]. The addition of adjuvants to local anesthetics can achieve the above configuration without affecting the effect of epidural analgesia [1,2].

Local anesthetics commonly used for epidural labor analgesia include bupivacaine and ropivacaine. In this study, ropivacaine was

Table 3
Side effects.

		Fentanyl, 0.4 μg/ml (n = 40)	Dexmedetomidine, 0.4 μg/ml (n = 40)	Esketamine, 1.0 mg/ml (n = 40)	*P* value
Hypotension		0	0	1	0.33
Nausea and Vomiting		1	0	0	0.33
Pruritus[a]		9	0	0	<0.01
Bradycardia		0	0	0	>0.99
Maternal Fever		0	1	0	0.33
Respiratory depression		0	0	0	>0.99
Excessive sedation		0	0	0	>0.99
Dizziness	Mild[b]	0	0	16[a]	<0.01
	Moderate	0	0	0	>0.99
	Severe	0	0	0	>0.99

Data are numbers.
[a] Group Fentanyl was different from Group Dexmedetomidine, and Group Esketamine (P = 0.002).
[b] Group Esketamine differed from Group Fentanyl, and Group Dexmedetomidine (P < 0.001).

chosen because of its less neurotoxcity and cardiotoxicity [23,24]. Numerous studies have shown that ropivacaine can be used safely and effectively for epidural labor analgesia [25,26]. Additionally, ropivacaine can also be covered by medical insurance and is widely used for epidural labor analgesia in China.

5. Limitation

Our study had some limitations. First, neither dexmedetomidine nor esketamine, used for epidural labor analgesia, has been approved by the Food and Drug Administration of America. Second, the results of our study may only be applicable to labor analgesia with 0.075 % ropivacaine, and other concentrations of ropivacaine need to be confirmed by further research. Third, we aimed to control maternal NRS scores to 3 or lower; However, most studies set NRS less than or equal to 1 as the control goal [27,28]. Different pain thresholds may result in different outcomes.

6. Conclusion

In conclusion, epidural dexmedetomidine was non-inferior compared with epidural fentanyl in combination with ropivacaine for PCEA during labor, in setting of the conditions of this study. Furthermore, we failed to demonstrate the non-inferiority of epidural esketamine to epidural fentanyl in combination with ropivacaine for labor analgesia.

Ethics declarations

This study was reviewed and approved by the Ethical Committee of Affiliated Xiaoshan Hospital, Hangzhou Normal University (Hangzhou, China) in February 2022, with the approval number: KL2022015. The protocol was registered in the Chinese Clinical Trial Registry on August 1, 2022 (https://www.chictr.org.cn/bin/project/edit?pid = 159765; ChiCTR2200062309). All patients provided informed consent to participate in the study. We confirm our study has complied the CONSORT guidelines.

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Data availability statement

The data of the patients in this study are not publicly available due to the ethical restriction. Data are available on reasonable request from the corresponding author.

Consent for publication

All authors have read and approved the manuscript, and agree to submit to your journal.

CRediT authorship contribution statement

Lifeng Ni: Writing – original draft, Data curation. **Shengjie Yao:** Formal analysis, Data curation. **Yahong Wu:** Data curation. **Jianxin Ni:** Data curation. **Qingtao Wang:** Data curation. **Zhong Mei:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition, Formal analysis. **Jing Yu:** Writing – review & editing, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e30218.

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