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CLINICAL TRIAL REPORT

Labor Analgesia Initiation with Dural Puncture Epidural versus Standard Epidural Techniques: A Prospective Randomized Dose Allocation Study of Ropivacaine

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Background: When compared to the standard epidural technique, the dural puncture epidural (DPE) technique is reported to provide quicker onset of labor analgesia and improved quality of analgesia. Recently, the DPE technique was found to lower the effective dose for 90% (ED90) of patients receiving bupivacaine for labor analgesia by 35%. However, key pharmacological differences between bupivacaine and ropivacaine and the effect of a DPE technique on ropivacaine doses have not been studied. Therefore, we aimed to determine the effective dose for 50% (ED50) and ED90 of ropivacaine for labor analgesia in parturients when initiated with the DPE and standard epidural techniques.

Methods: Study participants were randomized to receive one of the five doses of ropivacaine (12, 15, 18, 21, and 24 mg) undergoing one of the two epidural techniques (either a DPE or standard epidural technique). A total volume of 20 mL of local anesthetic was administered epidurally. Effective analgesia was defined as the patient reporting an NRS pain score < 3 at 20 minutes following drug administration. The ED50 and ED90 values of epidural ropivacaine for labor analgesia were determined using probit analysis, and comparisons were made using the relative median potency ratio.

Results: The ED50 of ropivacaine for initiating labor analgesia using the DPE vs standard epidural techniques was 18.6 mg (95% CI, 16.4 to 21.1 mg) vs 19.2 mg (95% CI, 17.0 to 21.8 mg), respectively. The ED90 values were 30.5 mg (95% CI, 26.6 to 38.3 mg) vs 31.1 mg (95% CI, 27.1 to 39.2 mg), respectively. The relative median potency ratio for ropivacaine with DPE vs standard epidural technique was −0.6 (95% CI, −4.0 to 2.6).

Conclusion: Our findings suggest that there is no dose-sparing effect of ropivacaine when using the DPE technique vs a standard epidural technique for labor analgesia.

Keywords: labor analgesia, dural puncture epidural, standard epidural, ropivacaine, dose–response

Introduction

The dural puncture epidural (DPE) is a technique, which is reported to provide quicker onset of labor analgesia, improved quality of analgesia, and a local anesthetic drug-sparing effect when compared to the standard epidural technique.[1–5] Regarding mechanism of action, the currently accepted theory is that the spinal needle creates a conduit for epidurally administered medications to move into the subarachnoid space, thereby resulting in a partial spinal analgesic effect. However, the benefits of implementing the DPE technique for labor analgesia remain a subject of debate, because the existing literature on this issue remains inconclusive.[6–9] Recently, Maeda et al[10] found that the DPE technique for labor analgesia lowers the effective dose for 90% (ED90) of patients receiving a bupivacaine loading dose by 35%, implying that an important benefit of the DPE technique is providing a dose-sparing effect of the epidural local

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anesthetic. While ropivacaine's similar biochemical structure means that the clinical effects of ropivacaine and bupivacaine are very comparable, there are key pharmacological differences in drug efficacy between the two drugs that justify a similar study characterizing the ED90 of ropivacaine. Furthermore, many institutions use ropivacaine as the primary local anesthetic for labor analgesia instead of bupivacaine; therefore, characterizing the ED90 of ropivacaine is of particular interest to such institutions.

In this study, we performed a prospective, double-blind, randomized trial to evaluate the ED50 and ED90 of ropivacaine for labor analgesia when initiated with either the DPE technique or the standard epidural technique. We hypothesized that the DPE technique would reduce the dose of ropivacaine required for effective analgesia when compared to the standard epidural technique.

Materials and Methods

Ethics

This study was approved by the Ethics Committee in Jiaxing University Affiliated Women and Children Hospital (2024-Y-30) and registered on June 17, 2024 (registration number, ChiCTR2400085730) in the Chinese Clinical Trial Registry (https://www.chictr.org.cn). All study participants provided written informed consent. Participant recruitment lasted from July 1, 2024 to December 18, 2024. This study complies with the Declaration of Helsinki.

Patients and Setting

Women with a singleton pregnancy requesting neuraxial labor analgesia were eligible for study participation. Inclusion criteria were American Society of Anesthesiologists (ASA) physical status II or III, maternal age 20–40 years, gestational age 37–42 weeks', cervical dilation 2–5 cm, and Numeric Rating Scale (NRS) pain score ≥5 (where 0 indicated no pain and 10 indicated worst pain imaginable). Exclusion criteria were contraindications to neuraxial analgesia, obstetric pathology, severe medical comorbidities, administration of opioids or sedatives within 4 hours prior to requesting labor analgesia, allergy to investigation drugs, and inability to comprehend and respond with an NRS pain score.

Study Protocol

Participants were randomly assigned to receive one of five doses of ropivacaine undergoing one of the two epidural techniques (either a DPE or standard epidural technique), resulting in a total of 10 distinct randomization groups. Ropivacaine doses used were 12, 15, 18, 21, and 24 mg (The doses were selected based on prior data from our institution.[11] And to ensure a comprehensive evaluation of the dose–response relationship, the chosen dose range was designed to encompass a broad segment of the dose–effect curve), all of which were diluted in a total volume of 20 mL normal saline.

The randomization sequence was generated using computer-generated random numbers in Microsoft Excel (Microsoft, Redmond, Washington, USA). Randomization assignments were placed in opaque envelopes prior to starting the study by an independent research assistant who was not involved in clinical care. Envelopes were opened at the time of enrollment of each participant.

Prior to beginning the neuraxial technique, each patient was placed in a left lateral decubitus position and a nurse-initiated monitoring of non-invasive blood pressure, pulse oximetry, and external tocodynamometry. Neuraxial techniques were placed by one of the four experienced anesthesiologists (FYD, JYH, YG, and HJH). Following skin disinfection and administration of 3 mL of 2% lidocaine subcutaneously, a 17-gauge Tuohy needle was inserted at the estimated L3-4 vertebral interspace. The loss-of-resistance to saline technique was used to localize the epidural space.

For study subjects who were randomized to have a DPE technique, a 25-gauge Whitacre needle was passed through the Tuohy needle using the needle-through-needle technique. Upon confirmation of clear cerebrospinal fluid (CSF) flow, the spinal needle was withdrawn and a 19-gauge, wire-reinforced multi-orifice epidural catheter was advanced 4–5 cm into the epidural space with the Tuohy needle bevel-oriented cephalad. In cases of absent CSF flow, both needles were withdrawn, and the procedure was repeated. If CSF continued to be absent, then the patient was excluded from the study, and further clinical care was at the discretion of the attending anesthesiologist.

For study subjects who were randomized to have a standard epidural technique, the same protocol was followed as for the DPE technique with the exception of passage of the Whitacre needle.

For the accuracy of the study, we opted not to use the standard regimen of lidocaine mixed with epinephrine as the test dose, because 1.5% lidocaine (45 mg) may interfere with the dose–effect relationship of ropivacaine for analgesia. Instead, 5 mL of the randomly assigned study drug was administered epidurally as a test dose over 10 seconds. After observing a negative response to the test dose for two minutes, the remaining 15 mL of study drug was administered epidurally over 30 seconds. The anesthesiologist then left the room and another anesthesiologist who was blinded as to randomization group entered the room to assess effectiveness.

Effective analgesia was defined as the patient reporting an NRS pain score < 3 at 20 minutes following drug administration. In cases where no uterine contraction occurred at 20 minutes after drug administration, an NRS score < 3 during either the preceding or subsequent contraction was deemed indicative of effectiveness. Ineffective analgesia was defined as the patient reporting an NRS pain score ≥ 3 at 20 minutes following drug administration. Those with ineffective analgesia were given a 10 mL rescue bolus of 0.25% ropivacaine. If fifteen minutes after rescue bolus administration, the patient continued to report ineffective analgesia, then the patient was excluded from the study and further clinical care was at the discretion of the attending anesthesiologist.

Sixty minutes after first administration of ropivacaine, an epidural infusion pump (Apon MC ZZB-IV, Jiangsu Apon Medical Technology Co., Ltd., Jiangsu, China) was started on a programmed intermittent epidural bolus (PIEB) setting with patient-controlled epidural analgesia (PCEA). Configuration parameters to administer ropivacaine 0.125% with sufentanil 0.3 μg/mL were as follows: 8 mL programmed bolus every 40 minutes, 8 mL PCEA dose with lockout interval of 15 minutes, and a maximum hourly limit of 40 mL. For breakthrough pain, 10 mL of 0.25% ropivacaine were administered.

Outcomes

The primary outcome was effective analgesia. Secondary outcomes included absolute NRS pain score, sensory block level, and Bromage score, all measured at 20 minutes following initial drug administration. Patient satisfaction was assessed one hour after delivery using a ten-point Likert scale, where 1 denoted complete dissatisfaction and 10 indicated the highest level of satisfaction. Other secondary outcomes included total consumption of ropivacaine, details regarding the administration of epidural analgesia (PCEA, PIEB, and manual bolus injections), adverse effects (nausea, vomiting, pruritus, and hypotension), as well as obstetric and neonatal outcomes.

Statistical Analysis

The sample size was calculated using the Cochran-Armitage Trend Test implemented in PASS software (version 11.0.7; NCSS, LLC, Kaysville, Utah, USA). The estimation was based on preliminary data suggesting that among the five groups receiving initial ropivacaine doses of 12, 15, 18, 21, and 24 mg, the respective proportions of patients achieving effective analgesia were 20%, 30%, 40%, 50%, and 70%. A total of 90 patients (18 per group) were determined to provide 90% statistical power to detect a linear trend in the proportion of patients with effective analgesia across the groups, using a Z-test with continuity correction at a significance level of 0.05. To accommodate potential dropouts, the final sample size was increased to 125 patients for DPE or standard epidural group.

The Kolmogorov–Smirnov test was used to assess the normality of the distribution of continuous variables. Student's *t*-test was used for normally distributed continuous variables, and results were summarized as mean (standard deviation, SD). The Mann–Whitney *U*-test was used for non-normally distributed continuous data, and results were summarized as median (interquartile range). The chi-squared ($\chi 2$) test was used for categorical variables, and results were summarized as n (%). The ED50 and ED90 values of ropivacaine for labor analgesia were determined using probit analysis, and comparisons were made using the relative median potency ratio. Statistical analyses were performed using GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA) and IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA). Statistical significance was determined at a P value < 0.05.

Results

Patient recruitment is shown in the Consolidated Standards of Reporting Trials (CONSORT) diagram in Figure 1. A total of 276 patients were approached, of which 9 declined to participate and 17 did not meet inclusion criteria, resulting in 250 patients being randomized. Of those randomized, 5 had non-functioning epidural catheters and 4 had failure of DPE technique. The final analysis of the primary outcome included 241 patients whose demographic and baseline characteristics are summarized in Table 1.

The percentage of patients with effective labor analgesia initiated by the DPE and standard epidural technique is illustrated in Figure 2, indicating a dose-dependent relationship. The ED50 of ropivacaine for initiating labor analgesia using the DPE vs standard epidural techniques was 18.6 mg (95% CI, 16.4 to 21.1 mg) vs 19.2 mg (95% CI, 17.0 to 21.8 mg), respectively. The ED90 of ropivacaine for initiating labor analgesia using the DPE vs standard epidural techniques was 30.5 mg (95% CI, 26.6 to 38.3 mg) vs 31.1 mg (95% CI, 27.1 to 39.2 mg), respectively. The relative median potency ratio for ropivacaine with DPE vs standard epidural technique was −0.6 (95% CI, −4.0 to 2.6), indicating a negligible difference between groups. The dose–response curves of ropivacaine for the initiation of labor analgesia, as

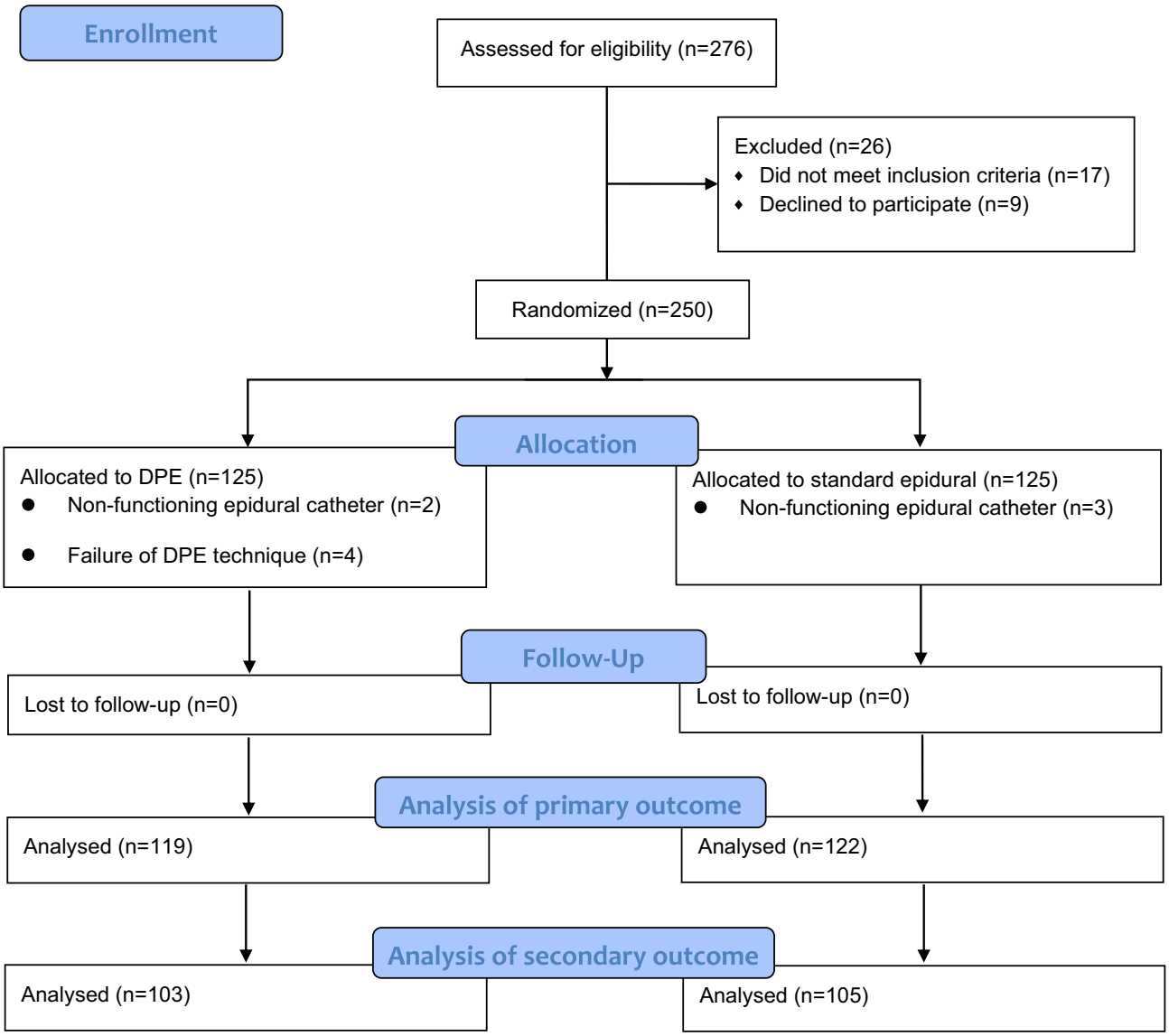

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram showing patient recruitment.

Table 1 Demographic and Baseline Characteristics

	Dural Puncture Epidural (n = 119)	Standard Epidural (n = 122)	*P* value
Age (years)	28.8±4.1	28.7±3.9	0.82
Weight (kg)	72.0±11.1	72.6±10.2	0.64
Height (cm)	162.1±4.5	162.2±4.2	0.95
Body mass index (kg/m^2)	27.3±3.7	27.6±3.4	0.59
Gestational age (weeks')	39.3±0.8	39.3±0.9	0.71
Nulliparity	91 (76.5)	90 (73.8)	0.66
Induction of labor	83 (69.7)	77 (63.1)	0.34
At time of neuraxial technique placement			
NRS pain score	8.5±1.1	8.5±1.1	0.86
Cervical dilation (cm)	2 (2–2)	2 (2–2)	0.95
Dose of oxytocin infusion (u/h)	0.34±0.16	0.38±0.20	0.24

Notes: Data are presented as mean (standard deviation), median (IQR), or number (%).
Abbreviation: NRS, Numeric rating scale.

derived through probit regression analysis, are presented in Figure 3. The results of the Pearson goodness-of-fit χ2 test indicated that the probit model exhibited an adequate fit (P = 0.39).

Secondary outcomes are summarized in Table 2. Data for 33 patients (16 patients from the DPE group and 17 patients from the standard epidural group) were excluded from the analysis of secondary outcomes due to intrapartum cesarean delivery. There were no statistically significant differences in the analgesia characteristics between the two groups, including thoracic

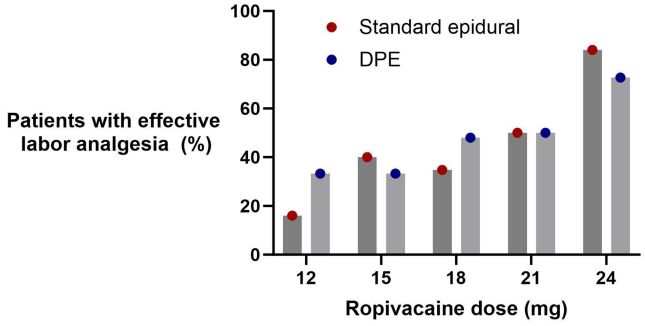

Figure 2 The percentage of patients with effective labor analgesia initiated by the DPE and standard epidural techniques.

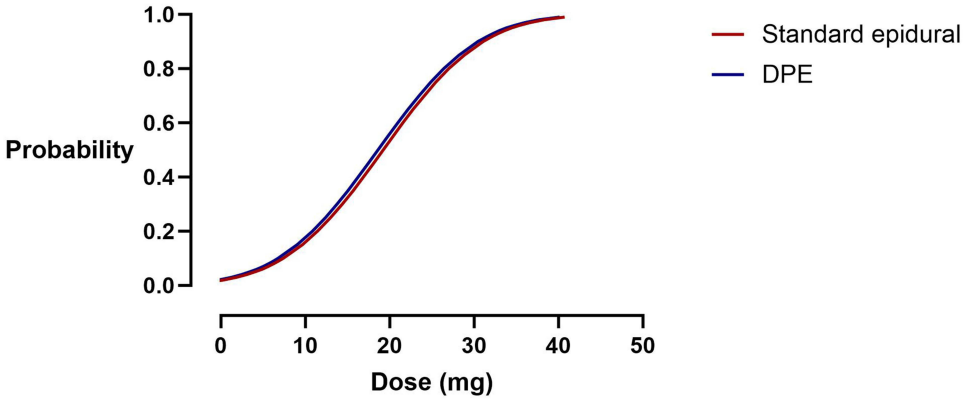

Figure 3 The dose–response curve of epidural ropivacaine for the initiation of labor analgesia.

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Table 2 Secondary Outcomes

	Dural Puncture Epidural (n = 103)	Standard Epidural (n = 105)	*P* value
Sensory block level at 20 minutes	T10 (T8-T10)	T10 (T8-T11)	0.07
Bromage score > 0 at 20 minutes	2 (5.9)	2 (4.9)	0.78
Duration of labor analgesia (minutes)	350 (232–475)	332 (241–457)	0.77
Patients requiring PCEA	4 (3.9)	12 (11.4)	0.07
Number of PCEA boluses required	1 (1–1.75)	1 (1–1)	0.68
Provider boluses	6 (5.04)	7 (5.74)	0.81
Total consumption of ropivacaine (mg)	77.5 (55.6–119.1)	81.3 (58.7–116.2)	0.47
Hourly consumption of ropivacaine (mg)	15.5 (12.1–18.8)	16.6 (14.2–20.2)	0.06
Catheter manipulation for unilateral block	2 (2)	0 (0)	0.24
Delivery mode			
Vaginal delivery	90 (87.4)	91 (86.7)	0.85
Instrumented vaginal delivery	13 (12.6)	14 (13.3)	0.89
Duration of first stage of labor (minutes)	437 (306–650)	443 (301–630)	0.52
Duration of second stage of labor (minutes)	52 (0–105)	63 (21–124)	0.22
Adverse events			
Postpartum headache	0 (0)	0 (0)	–
Pruritus	12 (11.7)	8 (7.6)	0.36
Shivering	18 (17.5)	16 (15.2)	0.66
Nausea	15 (14.6)	14 (9.5)	0.48
Vomiting	11 (10.7)	12 (11.4)	0.86
Hypotension	3 (2.9)	5 (4.7)	0.50
Prolonged deceleration	9 (8.7)	8 (7.6)	0.81
Apgar score at 1 minute	10 (10–10)	10 (10–10)	0.66
Apgar score at 5 minutes	10 (10–10)	10 (10–10)	0.95
Patient satisfaction	10 (9–10)	10 (9–10)	0.39

Notes: Data are presented as mean (standard deviation), median (interquartile range), or number (%).
Abbreviation: PCEA, patient controlled epidural analgesia.

sensory block level at 20 minutes, Bromage score > 0 at 20 minutes, number of patients requiring PCEA, provider manual boluses, total or hourly consumption of ropivacaine, and catheter manipulation for unilateral block, as well as side effects.

Discussion

In this prospective, randomized, double-blind dose-finding study, we determined that the ED50 of ropivacaine for initiating labor analgesia using the DPE vs standard epidural techniques was 18.6 mg vs 19.2 mg, respectively, while the ED90 was 30.5 mg and 31.1 mg, respectively. We also found that unilateral block, total ropivacaine consumption, adverse events, Apgar scores, and patient satisfaction were not different based on epidural or DPE technique used.

The finding that the ED50 and ED90 of ropivacaine for initiating labor analgesia was similar with both a DPE and standard epidural technique was unexpected and surprising. A recently published biased-coin sequential allocation study by Maeda et al[10] reported that the ED90 of bupivacaine for initiating labor analgesia using the DPE technique was 35% lower dose compared to the standard epidural technique. Given the similar chemical structures and dose–response profiles of ropivacaine and bupivacaine, we were expecting a similar reduction of the ED90 of ropivacaine in parturients randomized to the DPE technique.

One reason for the difference in our results compared to Maeda et al[10] may be related to slight differences in study protocol. While both studies used a total volume of 20mL of local anesthetic, in our study we administered a 5mL "test dose" followed by 15mL bolus compared to the Maeda et al[10] study in which the total volume was administered in 5mL increments. It is possible that this difference in local anesthetic administration protocol could result in a different

mechanism by which the DPE technique works. Therefore, future studies on different local anesthetic administration protocols with DPE should be performed to further characterize the mechanism by which the DPE technique works.

There are several other differences in our study protocol that might also explain our findings. Our study used a multi-orifice catheter, while Maeda et al used a single-orifice catheter. We measured effective analgesia at 20 minutes after local anesthetic administration compared to 30 minutes in the Maeda et al[10] study. Positioning was also different; Maeda et al performed the neuraxial techniques in a sitting position, while we performed the techniques in a lateral decubitus position. Administration in the sitting position is more likely to spread to the sacrococcygeal region due to the effect of gravity, whereas administration in the lateral decubitus position tends to spread toward the thoracic region. This is because, in pregnant women, the width of the hips is typically greater than that of the shoulders, resulting in a slight head-down tilt when lying in the lateral position.[12] Multiple studies have found that the volume of local anesthetic, the pressure applied during its administration, the distance from the dural puncture site to the tip of the epidural catheter, and the gauge of the spinal needle all influence the distribution of local anesthetic.[4,7,8,13] Therefore, it is possible that some or even most of the protocol differences in our study could have potentially affected the results. Regardless, it may be worth repeating studies with similar protocols to gain a better understanding of the dose–response curves of ropivacaine and bupivacaine in the setting of DPE vs standard epidural techniques.

Another interesting finding was that the DPE technique was not associated with a decreased incidence of unilateral block compared to the standard epidural technique. Prior studies[2,3] have suggested that the DPE technique may reduce the incidence of unilateral block, thereby improving the overall quality of labor analgesia. However, not all studies have found this to be the case.[6,7] Furthermore, a recent meta-analysis failed to identify a significant benefit of the DPE technique for decreasing unilateral block. Therefore, further studies are necessary to investigate whether the DPE technique exerts an influence on the functionality of the epidural catheter, and whether or not the local anesthetic administration protocol may also play a role in the observed effects.

There is ongoing debate regarding the advantages of a DPE technique for labor analgesia. Layera et al[8] conducted a meta-analysis and concluded that the current evidence supporting the routine use of DPE for labor analgesia remains inconclusive. Heesen et al[9] similarly concluded from their meta-analysis that there is insufficient evidence to determine the benefits and risks associated with the DPE technique. In our study, we found similar requirements for provider-administered epidural boluses, PCEA boluses, total and hourly ropivacaine consumption, and incidence of catheter manipulation for unilateral block with both techniques, a finding that is consistent with one of our prior studies as well.[6] Therefore, it is premature to provide a recommendation for or against its routine application in clinical practice. Regardless, the DPE technique does appear to be a valuable adjunct in cases where the loss of resistance technique does not definitively confirm that the Tuohy needle is in the epidural space.

The finding that the ED90 determined in this study was significantly lower than that reported in previous studies was unexpected. Lee et al[14] conducted a dose–response study to estimate the ED50 and ED95 of epidural ropivacaine for initiating labor analgesia using probit regression analysis. In their study, patients were randomly assigned to receive 10 mL of ropivacaine at doses of 10, 20, 30, 40, and 50 mg (corresponding concentrations of 0.1%, 0.2%, 0.3%, 0.4%, and 0.5%) as the initial loading dose. The effective dose was defined as the dose that reduced the pain score to 50% or less of the baseline value within 30 minutes following epidural drug administration. The authors determined that the ED95 of epidural ropivacaine for labor analgesia was 55.9 mg. Similarly, Ngan Kee et al,[15] using the same definition of an effective dose, compared 20 mL of ropivacaine at doses of 7, 15, 20, 30, 45, and 60 mg (corresponding concentrations of 0.035%, 0.075%, 0.1%, 0.25%, and 0.3%) for epidural labor analgesia, and found the ED95 of epidural ropivacaine for labor analgesia was 40.6 mg using non-liner regression. It is challenging to elucidate the differences in results among these studies. However, factors such as varying definitions of effective dose, contrasting study protocols, and differences in statistical analysis methods may contribute to the observed variability across studies. In addition, the absence of opioids in other studies represents the most significant difference compared to our study, as opioids decrease the required dose of epidural local anesthetics.

While our study methodology was strong, it is important to consider the limitations as well. First, the ED90 of epidural ropivacaine fell outside the dose range examined in this study and was estimated using Probit analysis; therefore, it necessitates additional clinical validation prior to routine implementation in clinical practice. Second, we used probit analysis and compared results using the relative median potency ratio. While the statistical methodology is

robust, it is possible that centered isotonic regression might offer different results. Third, the primary outcome was assessed 20 minutes after the initial loading dose, but we did not compare the difference in onset time between the DPE and standard epidural techniques. Since prior reports[1,4,16] indicate that the onset time for labor analgesia using a DPE technique is 2 minutes faster than with a standard epidural technique, we did not consider this minor difference clinically significant enough to warrant re-evaluation in this study.

In summary, the findings of our study suggest that there is no dose-sparing effect of ropivacaine when using the DPE technique for labor analgesia.

Abbreviations

ASA, American Standards Association; DPE, dural puncture epidural; ED50, Median effective dose; ED90, 90% effective dose; NRS, Numeric Rating Scale; CSF, cerebrospinal fluid.

Data Sharing Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy policy but are available from the corresponding authors on reasonable requests.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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