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CLINICAL TRIAL REPORT

# Determination of Median Effective Concentration ($EC_{50}$) of Ropivacaine with Adjuvant Dexmedetomidine When Using the Dural Puncture Epidural Technique for Labor Analgesia: An Up-Down Sequential Allocation Study

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**Background:** The dural puncture epidural (DPE) technique offers a promising option for managing labor pain. While dexmedetomidine has proven clinically efficacious in labor pain, its optimal concentration in DPE technique remains underexplored. This trial was designed to identify the ideal adjuvant concentration of dexmedetomidine to ropivacaine in the DPE technique for labor analgesia.

**Methods:** Parturients were randomly allocated to six groups receiving different concentrations of dexmedetomidine (0, 0.1, 0.2, 0.3, 0.4, and 0.5 μg/mL). In each group, ropivacaine was initiated at 0.1% concentration. Effective analgesia was defined as visual analog scale scores ≤ 3 during two consecutive uterine contractions within 30 minutes; if achieved, the ropivacaine concentration for subsequent parturients was reduced by 0.01%, otherwise increased by 0.01%.

**Results:** The median effective concentrations of ropivacaine at dexmedetomidine concentrations of 0.3, 0.4, and 0.5 μg/mL were 0.042% (95% CI: 0.035%–0.049%), 0.036% (95% CI: 0.030%–0.043%), and 0.037% (95% CI: 0.030%–0.044%), which were lower than those at 0, 0.1, and 0.2 μg/mL (0.079% [95% CI: 0.071%–0.088%], 0.070% [95% CI: 0.062%–0.078%], and 0.059% [95% CI: 0.053%–0.066%]). Comparisons between the three highest dexmedetomidine doses showed no significant differences. Scores on the Ramsay Sedation Scale were significantly elevated in the three highest concentration groups compared to the 0 and 0.1 μg/mL groups. Additionally, the scores for the 0.3 and 0.5 μg/mL groups exceeded that of the 0.2 μg/mL group. Comparisons involving the 0.2 μg/mL group versus the 0.4 μg/mL group, as well as those among the three highest concentration groups, all showed no statistical difference.

**Conclusion:** For labor analgesia using the DPE technique, 0.3 μg/mL dexmedetomidine is the optimal adjuvant concentration to ropivacaine, balancing analgesic efficacy and safety. Higher concentrations do not enhance analgesia but may increase the risk of sedation.

**Keywords:** dural puncture epidural technique, dexmedetomidine, median effective concentration, labor analgesia

## Introduction

The dural puncture epidural (DPE) technique, a novel refinement of the combined spinal-epidural technique, offers a promising option for managing labor pain.[1] This technique involves intentionally puncturing the dura, but without subsequent injection of any medication into the intrathecal space. Analgesia is subsequently initiated through drugs administered via an epidural catheter. Relative to the epidural technique, the DPE technique offers advantages including quicker onset, improved sacral spread, fewer unilateral or focal sensory blocks, and fewer catheter failures.[2–4] The

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improved analgesic performance of DPE likely stems from local anesthetics entering the subarachnoid space via the dural puncture site, where they exert a potentiating effect.[5]

Opioids are the most commonly used adjuvants in labor analgesia due to their ability to reduce local anesthetic requirements and enhance analgesic efficacy.[6] However, their administration is linked to notable adverse effects like pruritus, nausea, and vomiting, which can negatively impact maternal comfort and pose risks to both maternal and fetal safety, motivating the search for safer alternatives.[7] As a highly selective $\alpha_2$-adrenoceptor agonist, dexmedetomidine holds potential as an alternative to opioid adjuvants owing to its anxiolytic, sedative, and analgesic properties.[8] Within neuraxial anesthesia, the specific processes through which dexmedetomidine augments the analgesic potency of local anesthetics remain to be fully delineated. Existing studies have shown that dexmedetomidine can diffuse through the dura mater into the cerebrospinal fluid and act on presynaptic and postsynaptic membranes of spinal neurons. Activation of potassium ($K^+$) channels via G-protein signaling pathways induces neuronal membrane hyperpolarization, thereby reducing efferent sympathetic activity and effectively blocking pain signal transmission.[9,10] Furthermore, its safety and effectiveness have been demonstrated in both epidural and spinal anesthesia.[11,12] A recent pilot study comparing dexmedetomidine versus sufentanil as adjuncts in epidural labor analgesia demonstrated that dexmedetomidine provided superior pain relief and shortened the first stage of labor.[13] Nevertheless, higher concentrations of dexmedetomidine can produce undesirable motor blockade.[14,15] Thus, optimizing its concentration is essential to maximize therapeutic benefits, minimize adverse effects, and ensure comfort and safety for both mother and fetus during delivery.

The optimal concentration of dexmedetomidine in the DPE technique remains undetermined. Although 0.4 μg/mL dexmedetomidine has been suggested as optimal for conventional epidural labor analgesia,[16,17] whether this concentration is also ideal for the DPE technique remains unknown. Accordingly, this trial was conducted using a sequential allocation design to establish the median effective concentration ($EC_{50}$) of ropivacaine when combined with varying concentrations of dexmedetomidine via the DPE technique. We postulated that 0.3 μg/mL represents the most effective adjuvant concentration of dexmedetomidine for ropivacaine in DPE technique, and that exceeding this concentration does not provide extra analgesic benefit.

# Methods

## Design and Study Subjects

The sequential allocation study was approved by the Ethics Committee of Women and Children's Hospital, Qingdao University (QFELL-KY-2025-29), and was registered at the Chinese Clinical Trial Registry (ChiCTR2500108056). This research complies with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. A total of 180 pregnant women were enrolled between August 2025 and September 2025. Informed consent was obtained in writing from all parturients before enrollment.

Inclusion criteria: nulliparous women with a singleton term pregnancy (37–41 weeks of gestation), American Society of Anesthesiologists physical status I or II, in active spontaneous labor with the cervix dilated to 2–3 cm during the latent phase, and reporting a baseline visual analog scale (VAS) score exceeding 5 at the time of analgesia request.

Exclusion criteria: Women were excluded if age < 20 or > 35 years, had severe obesity (BMI ≥ 40 kg/m$^2$), presented with any contraindications for neuraxial blockade, had pregnancy-related complications (such as gestational hypertension, gestational diabetes, or preeclampsia), had conditions that might require cesarean delivery (such as placenta previa or uterine abnormalities), had severe comorbidities (such as cardiomyopathy, liver disease, renal insufficiency), or had known fetal malformations. Participants were excluded if they experienced accidental dural puncture, failed to obtain cerebrospinal fluid (CSF) return upon spinal needle insertion, or underwent delivery within 1 hour of epidural catheter insertion.

## Randomization and Blinding

A computer-generated randomization list was prepared by an independent researcher using Microsoft Excel. Using the randomization list, participants received solutions containing dexmedetomidine at one of the following concentrations: 0, 0.1, 0.2, 0.3, 0.4, or 0.5 μg/mL. The allocations were concealed in opaque, sequentially numbered envelopes. Immediately prior to analgesia, a different researcher, also independent of clinical care and outcome assessment, opened

the envelope and prepared the corresponding study drug. All solutions were identical in appearance. The anesthesia was administered by one of two anesthesiologists (HL, JWS), and all outcome assessments were conducted by an investigator, all of whom were blinded to group assignment.

## Intervention

Following admission to the delivery room, intravenous access was secured and maternal-fetal monitoring was initiated, including $SpO_2$, noninvasive blood pressure, electrocardiography (ECG), and fetal heart rate monitoring. Following positioning in the right lateral decubitus posture at the L3–L4 interspace, the epidural space was subsequently identified by employing a 17-gauge Tuohy needle and the loss-of-resistance technique. A 25-gauge spinal needle (Weigao Ruixin Medical Technology, Weihai, Shandong, China) was then used to perform dural puncture, and free CSF return was confirmed prior to threading an epidural catheter 4 cm into the epidural space. Analgesia was initiated only after confirming the absence of subarachnoid or intravascular catheter placement. To minimize interference with the results, no test dose was administered.

Each parturient received a 10 mL bolus of the study solution. For the first parturient in each group, the solution consisted of 0.1% ropivacaine plus a dexmedetomidine concentration allocated by randomization. In subsequent participants, the ropivacaine concentration was adjusted according to a sequential allocation design. This sequential design dictated that the ropivacaine concentration for the subsequent subject was adjusted based on the current participant's outcome: it was lowered by 0.01% following effective analgesia, or raised by the same increment if analgesia was ineffective. Subjects failing to achieve adequate pain relief within the 30-minute window were administered a supplemental 10 mL bolus of 1% lidocaine. If this rescue measure proved insufficient, these individuals were omitted from the final dataset, and the same ropivacaine concentration was administered to the next parturient.

The initial concentration was set at 0.1% ropivacaine, based on its documented efficacy for labor analgesia in previous studies and on its value for direct comparison with previous sequential allocation design.[13,17] Moreover, owing to the limited evidence on different dexmedetomidine concentrations in the DPE technique, the 0.1% ropivacaine baseline was selected to reduce potential maternal adverse effects while enabling a clearer differentiation of dexmedetomidine's analgesic contribution and associated side effects.

## Outcome

The primary outcome was effective analgesia, defined as a VAS score $\leq 3$ during two consecutive uterine contractions within 30 minutes. The VAS was scored from 0 (no pain) to 10 (worst pain imaginable). During each assessment, the parturient was asked about contractions, with confirmation via fetal monitoring findings.

Secondary outcomes were measured at 30 and 60 minutes after the initial solution. Evaluations included sensory block level (assessed with a wet cotton ball) and motor block extent (determined by the Bromage Scale: 0 = full leg joint mobility, 1 = the ability for flexion of knees and ankles, 2 = only ankle movement, 3 = complete leg joint immobility). The criteria for hypotension were set as a drop in systolic blood pressure by $\geq 20\%$ compared to baseline, or a systolic reading $< 90$ mmHg. We recorded the occurrence of nausea, vomiting, pruritus, respiratory depression ($SpO_2 < 90\%$), maternal bradycardia ($< 50$ bpm), prolonged fetal bradycardia ($< 110$ bpm for $> 10$ minutes), and sedation. Sedation was evaluated with the Ramsay Sedation Scale, where a score of 1 indicated anxiety/irritability; 2, alertness and orientation; 3, response to verbal commands; 4, response to light tactile stimulation; 5, no response to commands (deep sleep); and 6, no response to painful stimulation. Scores $\geq 4$ were deemed indicative of excessive sedation. Additionally, the durations of the first and second stages of labor were measured. For the newborn, we assessed the 1- and 5-minute Apgar scores and umbilical artery pH. Data on the delivery mode (vaginal or cesarean) were collected separately. Parturients were monitored for potential complications such as headaches on the first day postpartum.

## Sample Size and Statistical Analysis

Previous studies indicate that observing six pairs of sequence reversals in 20 to 40 patients yields a stable estimate of the $EC_{50}$.[18] Accordingly, this study enrolled 30 parturients per group, totaling 180 participants.

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The $EC_{50}$ of ropivacaine was estimated by calculating the mean concentration at all transition points (from ineffective to effective analgesia) within the sequential design. Comparisons of $EC_{50}$ values across groups were conducted with one-way analysis of variance (ANOVA), followed by pairwise post–hoc testing with the Holm–Šídák method. $P < 0.05$ was considered statistically significant. The overlapping confidence intervals (OCI) method was used as a supplementary analysis, where non-overlap of the 83% confidence intervals was considered indicative of a statistically significant difference.[19] Probit analysis was utilized for sensitivity analysis, with the corresponding dose–response curves created.

IBM SPSS Statistics for Windows version 27 (IBM Corp, Armonk, NY, USA) and GraphPad Prism 9.5 (GraphPad Software Inc, San Diego, CA, USA) were used to perform statistical analyses. Normality was assessed using the Kolmogorov–Smirnov test. Data with normal distribution are reported as mean ± SD and analyzed with ANOVA, followed by the Holm–Šídák post–hoc test, whereas non–normal data are presented as median (IQR) and analyzed using the Kruskal–Wallis test, with Dunn's test applied for post-hoc comparisons as needed. Categorical variables were presented as frequencies (percentages), with between-group comparisons made via the Cochran–Armitage trend test. $P < 0.05$ defined statistical significance.

## Results

Between August and September 2025, 214 parturients were assessed for eligibility. Ultimately, 180 eligible parturients were analyzed. The study flow diagram is presented in Figure 1. Participant demographic characteristics are listed in Table 1.

Figure 2 illustrates the sequential allocation results across varying concentrations of dexmedetomidine. Table 2 provides a comprehensive listing of the $EC_{50}$ values for each group. $EC_{50}$ values decreased with increasing dexmedetomidine concentrations. Post-hoc analysis using the Holm-Šídák test detailed the specific inter-group differences: no statistically significant difference in $EC_{50}$ was observed between the two lowest-concentration groups (0 and 0.1 μg/mL).

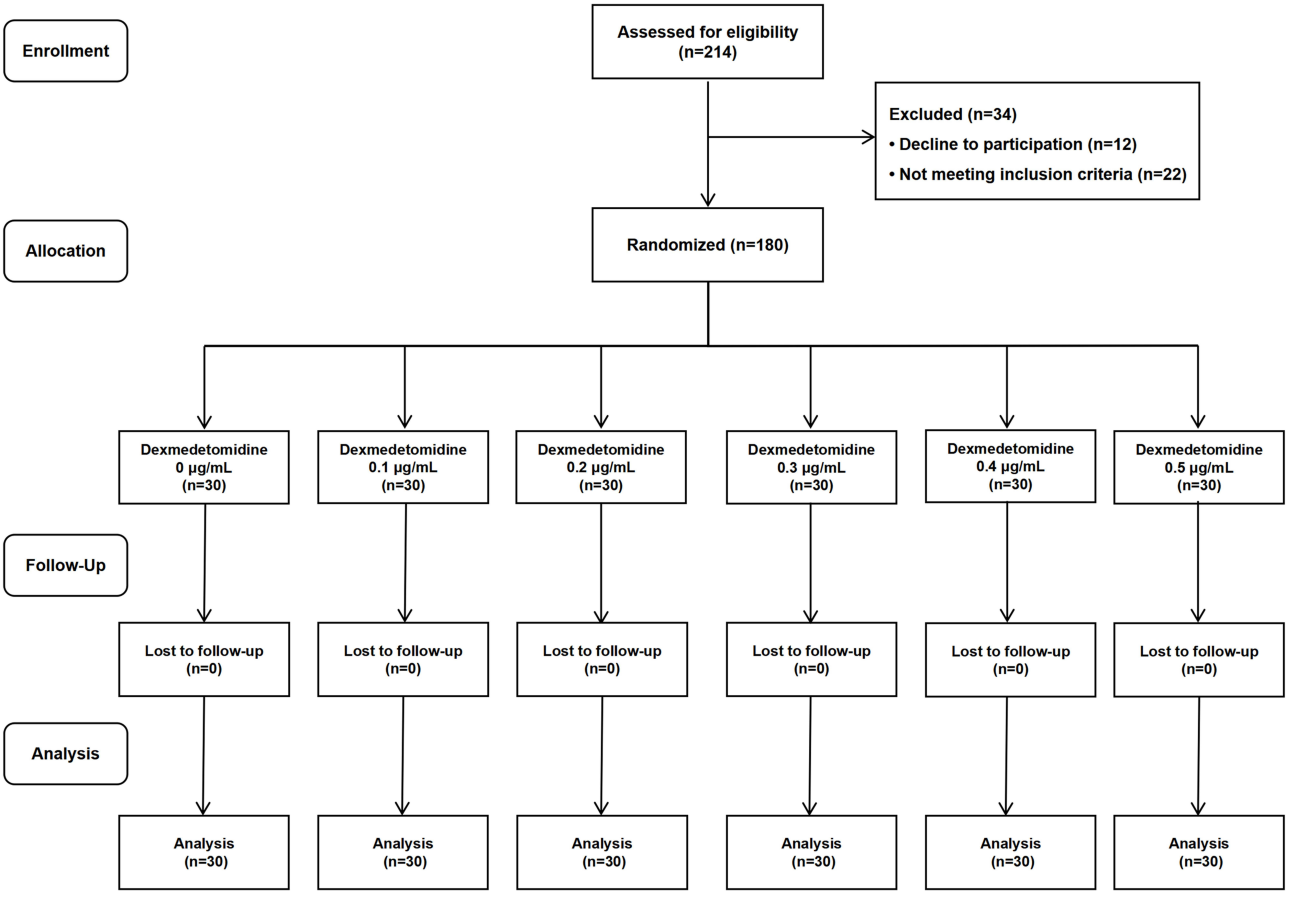


**Figure 1** Study flow diagram.

**Table 1** Demographic Characteristics Data

| | Dexmedetomidine 0 μg/mL (n=30) | Dexmedetomidine 0.1 μg/mL (n=30) | Dexmedetomidine 0.2 μg/mL (n=30) | Dexmedetomidine 0.3 μg/mL (n=30) | Dexmedetomidine 0.4μg/mL (n=30) | Dexmedetomidine 0.5 μg/mL (n=30) |
|---|---|---|---|---|---|---|
| Age (years) | 28 ± 3 | 29 ± 3 | 29 ± 3 | 29 ± 2 | 29 ± 3 | 29 ± 3 |
| Height (cm) | 164 ± 6 | 163 ± 6 | 164 ± 5 | 163 ± 5 | 164 ± 5 | 163 ± 5 |
| Weight (kg) | 75 ± 7 | 71 ± 8 | 73 ± 6 | 73 ± 6 | 74 ± 7 | 73 ± 7 |
| Body mass index ($kg/m^2$) | 28 ± 2 | 27 ± 2 | 27 ± 2 | 27 ± 2 | 27 ± 2 | 27 ± 2 |
| Gestational age (weeks) | 39 ± 1 | 39 ± 1 | 39 ± 1 | 39 ± 1 | 39 ± 1 | 39 ± 1 |
| Cervical dilation (cm) | 2 (2, 3) | 2 (2, 3) | 2 (2, 3) | 2 (2, 3) | 2 (2, 3) | 2 (2, 3) |
| Baseline VAS score | 7 (7, 8) | 7 (7, 9) | 7 (7, 9) | 7 (7, 8) | 7 (7, 8) | 7 (7, 8) |

**Note**: Data are presented as mean ± standard deviation or median (interquartile range).
**Abbreviation**: VAS, Visual Analogue Scale.

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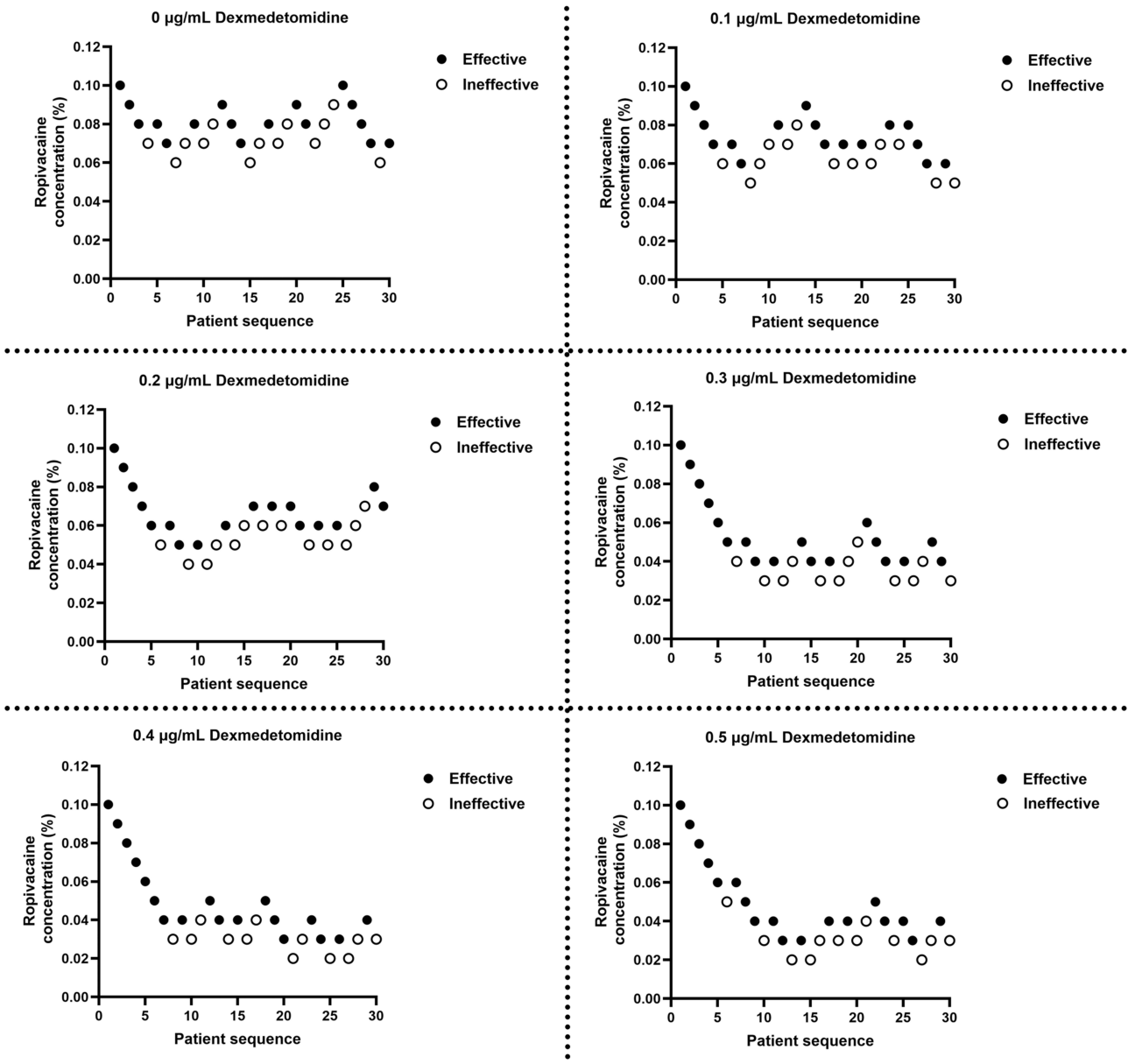


**Figure 2** Individual response to concentration of ropivacaine in 6 different concentrations of dexmedetomidine when using dural puncture epidural technique for labor analgesia.

**Note**: ● represents effective ○ represents ineffective.

The 0.2 μg/mL group exhibited a lower $EC_{50}$ than the 0 μg/mL group but showed no statistical difference from the 0.1 μg/mL group. In contrast, all three high-concentration groups (0.3, 0.4, and 0.5 μg/mL) showed $EC_{50}$ values that were significantly lower than those of the other three groups. But no significant differences were observed among the three high-concentration groups. The OCI method was employed as a supplementary analysis to analyze the confidence intervals, and the results were found to be consistent with those presented above.

Secondary outcomes are summarized in Table 3. Analysis of RSS scores revealed that no significant difference was observed between the two lowest-concentration groups (0 and 0.1 μg/mL). The 0.2 μg/mL group exhibited a significantly higher score than the 0 μg/mL group, but not the 0.1 μg/mL group. All three high-concentration groups (0.3, 0.4, and 0.5 μg/mL) scored significantly higher than both the two lowest-concentration groups. Furthermore, the scores in the 0.3 and 0.5 μg/mL groups were also significantly higher than that in the 0.2 μg/mL group, whereas the 0.4 μg/mL group did not differ from it. No significant differences in RSS scores were found among the three high-concentration groups

**Table 2** $EC_{50}$ of Ropivacaine with Varying Concentrations of Dexmedetomidine as Determined by the Sequential Allocation Method

| | Dexmedetomidine 0 μg/mL (n=30) | Dexmedetomidine 0.1 μg/mL (n=30) | Dexmedetomidine 0.2 μg/mL (n=30) | Dexmedetomidine 0.3 μg/mL (n=30) | Dexmedetomidine 0.4 μg/mL (n=30) | Dexmedetomidine 0.5 μg/mL (n=30) |
|---|---|---|---|---|---|---|
| $EC_{50}$ | 0.079% (CI: 0.071%-0.088%) | 0.070% (CI: 0.062%-0.078%) | 0.059% (CI: 0.053%-0.066%) | 0.042% (CI: 0.035%-0.049%) | 0.036% (CI: 0.030%-0.043%) | 0.037 (CI: 0.030%-0.044%) |

**Abbreviations**: $EC_{50}$, median effective concentration. CI, 95% confidence interval.

themselves. No between-group differences were detected in any other measured outcomes, including sensory and motor blockade, labor duration, neonatal parameters, delivery mode, or adverse events. No postpartum complications were reported.

Figure 3 presents the dose–response relationship of ropivacaine across the six dexmedetomidine concentration groups, with the $EC_{50}$ and $EC_{90}$ values determined by probit analysis.

## Discussion

Our study found that a dexmedetomidine concentration of 0.3 μg/mL is proposed as the optimal adjunct for DPE labor analgesia, achieving an advantageous equilibrium between analgesic potency and safety. This concentration yielded a ropivacaine $EC_{50}$ of 0.042% (95% CI: 0.035–0.049%), with no maternal or neonatal adverse events. Probit analysis yielded supportive values: $EC_{50}$: 0.039% (95% CI: 0.035%–0.044%); $EC_{90}$: 0.051% (95% CI: 0.045%–0.060%). Concentrations exceeding 0.3 μg/mL provided no incremental analgesic advantage but may increase the risk of sedation.

Numerous studies have confirmed that dexmedetomidine, when added as an adjuvant to ropivacaine, significantly enhances analgesic efficacy in epidural labor analgesia.[20,21] Tang et al demonstrated that in spinal anesthesia, dexmedetomidine as an adjunct to ropivacaine effectively improves analgesic potency while reducing ropivacaine dosage.[22] Ni et al conducted a study combining 0–0.5 μg/mL dexmedetomidine with 0.075% ropivacaine for epidural labor analgesia.[23] The optimal clinical outcomes were achieved with the regimen of 0.375 μg/mL dexmedetomidine combined with 0.075% ropivacaine, according to the findings of that study. However, this study lacked a sequential trial design to evaluate dexmedetomidine and ropivacaine combinations, leaving its applicability to other ropivacaine concentrations unconfirmed. A previous study indicated that 0.5 μg/mL dexmedetomidine was identified as the optimal concentration for epidural labor analgesia,[14] but its use of a 0.25 μg/mL incremental step indicated potential for improved precision. Liu et al explored optimal dexmedetomidine concentrations using a finer 0.1 μg/mL incremental strategy, finding that 0.4 μg/mL achieved the best clinical effect.[17] However, their focus on traditional epidural labor analgesia means its applicability to the DPE technique remains unclear. This study adopted the methodology of Liu et al,[17] using 0.1 μg/mL as the dexmedetomidine incremental step to investigate its effects at different concentrations in the DPE technique. Results showed that 0.3 μg/mL dexmedetomidine combined with DPE achieved optimal clinical efficacy. Unlike Liu et al, who used a 13 mL solution,[17] our study used a 10 mL volume, revealing lower $EC_{50}$ values at the same dexmedetomidine concentrations. This trend might be attributed to the analgesic-enhancing properties of the DPE technique, as prior studies have demonstrated its capacity to enhance drug delivery. The mechanism involves anesthetic transport from the epidural space to the subarachnoid space via the dural puncture site, thereby enhancing analgesia.[5] Notably, this process is influenced by multiple factors, including needle gauge, pharmacokinetic properties of the drug (such as molecular weight, lipophilicity, and diffusion coefficient), the epidural–subarachnoid pressure gradient, local anesthetic volume or concentration, the interval between dural puncture and drug injection, and injection pressure.[24] Therefore, further studies are needed to systematically clarify the interactions among these variables in order to optimize labor analgesia protocols.

In this study, RSS scores showed an increasing trend with rising dexmedetomidine concentrations. This observation likely results from the sedative action of dexmedetomidine on the locus coeruleus.[25] Evidence indicates that dexmedetomidine lowers perioperative stress hormones and augments sedative effects.[26] However, we observed that the RSS scores in the 0.3 μg/mL and 0.5 μg/mL groups were higher than those in the 0.2 μg/mL group, but the 0.4 μg/mL group did not differ significantly from the 0.2 μg/mL group. Several factors may explain this result. First, the sequential allocation design, while appropriate for estimating the $EC_{50}$, likely provided limited statistical power to detect subtle

**Table 3** Secondary Outcomes

| | Dexmedetomidne 0 μg/mL (n=30) | Dexmedetomidine 0.1 μg/mL (n=30) | Dexmedetomidine 0.2 μg/mL (n=30) | Dexmedetomidine 0.3 μg/mL (n=30) | Dexmedetomidine 0.4 μg/mL (n=30) | Dexmedetomidine 0.5 μg/mL (n=30) | *p* |
|---|---|---|---|---|---|---|---|
| Sensory block | 10 (8, 10) | 10 (8, 10) | 10 (10, 10) | 10 (8, 10) | 10 (8, 10) | 10 (8, 10) | 0.329 |
| Motor block (Bromage score >0) | 0 | 0 | 0 | 0 | 0 | 0 | |
| Hypotension | 1 (3.4%) | 0 | 2 (6.7%) | 2 (6.7%) | 1 (3.4%) | 2 (6.7%) | 0.398 |
| Pruritus | 1 (3.4%) | 1 (3.4%) | 2 (6.7%) | 0 | 2 (6.7%) | 3 (10%) | 0.272 |
| Nausea or vomiting | 2 (6.7%) | 1 | 2 (6.7%) | 3 (10%) | 2 (6.7%) | 4 (13.4%) | 0.255 |
| Maternal bradycardia | 1 (3.4%) | 0 | 1 (3.4%) | 2 (6.7%) | 0 | 0 | 0.555 |
| Respiratory depression | 0 | 0 | 0 | 0 | 0 | 0 | |
| Fetal bradycardia | 1 (3.4%) | 2 (6.7%) | 1 (3.4%) | 0 | 2 (6.7%) | 2 (6.7%) | 0.673 |
| RSS score | 2 (2, 2) | 2 (2, 2) | 2 (2, 3) | 3 (2, 3) | 2 (2, 3) | 3 (2, 3) | <0.001 |
| First stages of labor duration (min) | 433 ± 95 (n=28) | 440 ± 92 (n=28) | 406 ± 112 (n=29) | 393 ± 113 (n=27) | 389 ± 88 (n=29) | 371 ± 118 (n=30) | 0.097 |
| Second stages of labor duration (min) | 41 ± 8 (n=28) | 40 ± 7 (n=28) | 38 ± 10 (n=29) | 39 ± 11 (n=27) | 40 ± 11 (n=29) | 40 ± 10 (n=30) | 0.822 |
| 1 -minute Apgar score | 10 (9, 10) | 10 (9, 10) | 10 (9, 10) | 10 (9, 10) | 10 (9, 10) | 10 (9, 10) | 0.808 |
| 5 -minute Apgar score | 10 (10, 10) | 10 (10, 10) | 10 (10, 10) | 10 (10, 10) | 10 (10, 10) | 10 (9, 10) | 0.257 |
| Umbilical artery pH | 7.26 ± 0.07 | 7.24 ± 0.06 | 7.24 ± 0.06 | 7.23 ± 0.06 | 7.25 ± 0.07 | 7.25 ± 0.06 | 0.736 |
| Cesarean delivery | 2 (6.7%) | 2 (6.7%) | 1 (3.4%) | 3 (10%) | 1 (3.4%) | 0 | 0.272 |
| Postpartum headache | 0 | 0 | 0 | 0 | 0 | 0 | |

**Note**: Data are presented as number (percentage), median (interquartile range) or mean ± standard deviation.
**Abbreviation**: RSS score, Ramsay Sedation Scale score.


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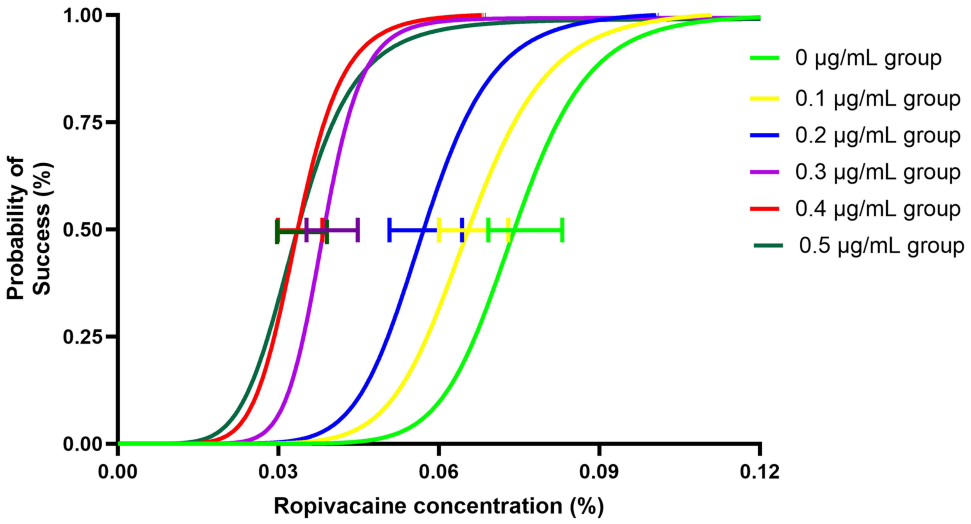


**Figure 3** Dose-response curve and 95% confidence interval for the $EC_{50}$ of ropivacaine at 6 different concentrations of dexmedetomidine when using dural puncture epidural technique for labor analgesia.

**Note**: The $EC_{50}$ and $EC_{90}$ values were: 0.074% (95% CI 0.067%–0.082%) and 0.095% (95% CI 0.086%–0.11%) for dexmedetomidine 0 μg/mL; 0.066% (95% CI 0.059%–0.073%) and 0.085% (95% CI 0.076%–0.098%) for dexmedetomidine 0.1 μg/mL; 0.057% (95% CI 0.051%–0.064%) and 0.074% (95% CI 0.066%–0.086%) for dexmedetomidine 0.2 μg/mL; 0.039% (95% CI 0.035%–0.044%) and 0.051% (95% CI 0.045%–0.060%) for dexmedetomidine 0.3 μg/mL; 0.034% (95% CI 0.030%–0.038%) and 0.043% (95% CI 0.038%–0.051%) for dexmedetomidine 0.4 μg/mL; and 0.034% (95% CI 0.030%–0.039%) and 0.044% (95% CI 0.039%–0.052%) for dexmedetomidine 0.5 μg/mL.

differences in secondary outcomes. Second, the RSS is a relatively coarse clinical tool with reduced sensitivity for discriminating mild sedation levels. Finally, the administration of only a single, relatively low dose of dexmedetomidine might have contributed to the lack of pronounced between-group differences. Dexmedetomidine is known to carry risks of excessive sedation and respiratory depression.[27,28] In this investigation, while the 0.5 μg/mL group presented with the greatest sedation scores, no participant in any group met the criteria for excessive sedation.

Although dexmedetomidine is not approved by the US Food and Drug Administration for intrathecal techniques, its safety in epidural applications has been validated by several previous studies.[13,21,22] This investigation examined the safety of combining various concentrations of dexmedetomidine with ropivacaine when administered via the DPE technique for labor analgesia. In comparison with the 0 μg/mL group, the use of dexmedetomidine was not linked to an elevated rate of adverse events in either the mothers or their newborns. These observations strengthen the evidence that dexmedetomidine can be safely used as an adjunct for labor analgesia via the DPE technique. Future investigations should further assess the safety of dexmedetomidine in neuraxial anesthesia through short-term and long-term follow-up.

Despite several advantages of this study, certain limitations should be acknowledged. Primarily, given the exploratory nature of this research and the limited existing data on dexmedetomidine combined with the DPE technique, we adopted a cautious approach to maximize maternal and fetal safety by excluding parturients younger than 20 years or aged 35 years and above. Furthermore, this trial enrolled only primiparous women carrying singleton pregnancies, due to known physiological variations in labor duration and pain perception between primiparous and multiparous women as well as between singleton and multiple pregnancies. Therefore, the generalizability of our results to multiparous women or to those with multiple gestations may be limited. Secondly, the definition of effective analgesia as a VAS score $\leq 3$ during two consecutive contractions within 30 minutes may introduce bias, given individual variations in contraction frequency and the subjective nature of pain scoring. To improve the objectivity of efficacy assessment in future studies, we recommend combining patient-reported outcomes with objective physiological measures, such as neurophysiological monitoring or changes in maternal heart rate variability, to reduce reliance on subjective scales. Furthermore, a constraint inherent to the sequential allocation methodology is that the sample size, though appropriate for determining the $EC_{50}$, might provide limited statistical power to identify significant variations in secondary outcomes, including sedation scores assessed by the RSS. Therefore, future research could consider including a larger sample size or conducting multi-center studies to comprehensively evaluate the effectiveness of dexmedetomidine in labor analgesia.


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## Conclusion

Although 0.4 μg/mL dexmedetomidine is regarded as optimal for epidural labor analgesia, this may not hold true for the DPE technique. Our research demonstrates that for labor analgesia using the DPE technique, 0.3 μg/mL dexmedetomidine is the optimal adjuvant concentration to ropivacaine, balancing analgesic efficacy and safety. Higher concentrations do not enhance analgesia but may increase the risk of sedation.

## Abbreviations

DPE, dural puncture epidural; VAS, visual analogue scale; $EC_{50}$, the median effective concentration; $EC_{90}$, the 90% effective concentration; CI, confidence interval; ANOVA, one-way analysis of variance; CONSORT, Consolidated Standards of Reporting Trials; ECG, electrocardiography; RSS, Ramsay Sedation Scale; BMI, Body mass index; CSF, cerebrospinal fluid; SpO, saturation of peripheral oxygen; OCI, overlapping confidence intervals.

## Data Sharing Statement

The data supporting the study findings are available from the corresponding author upon reasonable request.

## Ethics Approval and Informed Consent

The study was approved by the Ethics Committee of Women and Children's Hospital, Qingdao University (QFELL-KY-2025-29), and was registered at the Chinese Clinical Trial Registry (ChiCTR2500108056). All participants provided written informed consent. We confirm our study complies with the Declaration of Helsinki.

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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.

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## Disclosure

The authors report no conflicts of interest in this work.

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