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ORIGINAL RESEARCH

Determination of the Dose-Response Relationship of Epidural Dexmedetomidine Combined with Ropivacaine for Labor Analgesia

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Background: The safety and efficacy of dexmedetomidine for epidural labor analgesia have been reported in numerous literatures, but the optimal dose has not been fully determined. The objective of this study was to determine the dose-response relationship of epidural dexmedetomidine (combined with ropivacaine) for labor analgesia.

Methods: A total of 120 full-term laboring parturients requesting epidural labor analgesia were enrolled in the study from July 5, 2020 to September 22, 2021. The parturients were randomly assigned to receive 0, 0.1, 0.2, 0.3, 0.4 or 0.5 μg/mL dexmedetomidine combined with 0.075% ropivacaine epidurally. An effective dose was defined as numerical rating scale (NRS) pain score ≤3 at 30-minutes of epidural drug injection. The dose-response relationship of dexmedetomidine (with ropivacaine) for epidural labor analgesia was performed using probit regression. The median effective dose (ED_{50}) and the 95% effective dose (ED_{95}) values for epidural dexmedetomidine combined with 0.075% ropivacaine with 95% confidence intervals (CIs) were derived by interpolation.

Results: The estimated values of ED_{50} and ED_{95} with 95% CIs for epidural dexmedetomidine (combined with 0.075% ropivacaine) were 0.085 (0.015 to 0.133) μg/mL and 0.357 (0.287 to 0.493) μg/mL, respectively. No differences were found among groups for sensory block level, number of parturients with Bromage score >0, total dosage of analgesics, cesarean delivery rate, fetal birth weight, Apgar score at 1-minute, Apgar score at 5-minutes and adverse effects. Compared with other groups, group dexmedetomidine 0.5 μg/mL had a longer duration of the first stage of labor.

Conclusion: The ED_{50} and ED_{95} values of dexmedetomidine for epidural labor analgesia was 0.085 and 0.357 μg/mL under the conditions of this study. Dexmedetomidine is a suitable adjuvant for epidural labor analgesia.

Keywords: epidural, labor analgesia, dexmedetomidine, the dose-response relationship, ED_{50}, ED_{95}

Introduction

Epidural opioids added to local anesthetics are a commonly means of providing labor analgesia.[1–3] Nonetheless, opioid-related adverse effects (eg, nausea, vomiting and pruritus) may lead to maternal intolerable.[4,5] In contrast to opioids, dexmedetomidine has been used safely and effectively for epidural labor analgesia without increasing the incidence of adverse effects.[6–12] Consequently, it can be recommended that dexmedetomidine is used as an epidural adjuvant instead of opioids in some clinical circumstances, especially for parturients with opioid intolerance. Previous studies have reported the appropriate doses of epidural dexmedetomidine used for labor analgesia, whereas the optimal dose is

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unknown.[13,14] Before it is widely used in clinical practice, the epidural dose of dexmedetomidine should be fully determined.

The objective of this study was to determine the ED_{50} and ED_{95} of epidural dexmedetomidine for labor analgesia using probit regression.

Materials and Methods

Design and Study Subjects

This prospective, randomized and dose-finding study was approved by the Ethical Committee of Affiliated Xiaoshan Hospital, Hangzhou Normal University (Hangzhou, China) and was registered at the Chinese Clinical Trials (Registration number: ChiCTR2000034367). All parturients provided written informed consent.

120 full-term (37 ≥ weeks) laboring parturients requesting epidural labor analgesia were enrolled in the study from July 5, 2020 to September 22, 2021. Inclusion criteria were American Society of Anesthesiologists physical status (ASA) I or II, age 18 to 40 years, height 150 cm or greater, weight 100 kg or less, and baseline NRS pain scores > 3 (0 = no pain, 10 = worst pain). Exclusion criteria were as follows: allergy to amide-type local anesthetics or dexmedetomidine, bradycardia, multiple gestation pregnancies, pregnancy-induced hypertension or preeclampsia, known fetal abnormality and lack of informed consent.

Study Protocol

After arrival in the delivery room, each parturient was inserted an intravenous catheter. Subsequently, standard monitoring, including pulse oximetry, electrocardiography, non-invasive blood pressure and fetal heart rate was performed in each parturient.

A randomization code sequence was generated by an assistant who did not participate the following study using MedCalc 18.2.1 (MedCalc Software BV, Ostend, Belgium). The codes, were placed in numbered, opaque, sealed envelopes, randomly assigned parturients to one of six different doses of dexmedetomidine (Aibeining; Jiangsu Hengrui Co., Ltd.; 200 μg/ 2mL) with 0.075% ropivacaine (Naropin; AstraZeneca Co., Ltd.; 75 mg/ 10mL): 0, 0.1, 0.2, 0.3, 0.4 or 0.5 μg/mL dexmedetomidine.

A certified registered nurse anesthesia (CRNA) who was not involved in subsequent study performed the study solution preparation. Each dexmedetomidine dose, 75-mg ropivacaine and normal saline were mixed to a total volume of 100-mL injectate, then 10-mL loading dose was drawn into the identical 10-mL syringe and the rest 90-mL study solution was added into the infusion pump of patient controlled epidural analgesia (PCEA).

Parturients were placed in the left lateral position. After accomplishing aseptic precautions, skin and subcutaneous tissue was injected with 1% lidocaine. Epidural space was administered at the L2-3 vertebral interspace using an 18-gauge Tuohy needle and positioned using the loss-of-resistance-to-air technique. A reinforced epidural catheter was placed 3–4 cm into the epidural space and secured. The parturient was moved to the supine position, with left lateral uterine displacement. 10-mL study solution was then administered epidurally as a loading dose. The attending anesthesiologist who was blinded to the dose of the dexmedetomidine performed the epidural puncture and catheterization and injected the study solution.

The primary outcome was the effective rates of labor analgesia for different doses of dexmedetomidine with 0.075% ropivacaine at 30-minutes of epidural drug injection. An effective dose was defined as NRS pain score ≤ 3 at 30-minutes of epidural drug injection. Then the PCEA infusion pump was connected to maternal epidural catheter and switched on after 30-minutes of epidural drug injection. The background infusion rate was 3 mL/h, a bolus of 10-mL was administered when NRS pain score > 3 with a lockout interval of 20-minutes. An ineffective dose was defined as NRS pain score > 3 at 30-minutes of epidural drug injection. If pain relief was inadequate at 30-minutes of epidural drug injection, a 10-mL bolus of 1% lidocaine was administered, repeated at 15-minutes as required, and then the PCEA infusion pump was connected to epidural catheter.

NRS pain scores, non-invasive blood pressure, oxygen saturation, heart rate, and fetal heart rate was continuously monitored during this study. Sensory block (evaluated by pinprick), motor block (assessed using the Bromage scale),

onset of analgesia (was defined as the duration from the end of the epidural drug injection to NRS pain scores ≤ 3), duration of stage of labor, total dosage of analgesics, fetal birth weight and Apgar scores, were logged. Adverse effects included nausea, vomiting, pruritus, bradycardia, maternal fever (was defined as a tympanic temperature of ≥ 38 °C), and respiratory depression (a decrease of SpO2 to < 95%) were recorded. Excessive sedation was measured using Ramsay Sedation Scale. Hypotension (a decrease of mean systolic blood pressure to < 90 mmHg or to ≤ 80% of baseline), was treated with intravenous fluids and 6 μg norepinephrine as required.

Statistical Analysis

Sample size was determined using PASS 11 (NSCC, LCC, Kaysville, UT) (the Cochran-Armitage test for trend in proportions) and based on our initial pre-experiment in which the proportions of parturients with effective labor analgesia were 0.4, 0.5, 0.7, 0.8, 0.9 and 0.99 in parturients who received epidural dexmedetomidine at doses of 0, 0.1, 0.2, 0.3, 0.4 and 0.5 μg/mL combined with 0.075% ropivacaine, respectively. 13 parturients were required per group (Power 1-Beta: 0.99, Alpha Significance Level: 0.05), and in order to improve power the number of subjects was increased to 20 per dose group.[15]

SPSS 25.0 (IBM Corp, Armonk, NY) was used for statistical analysis. The Shapiro–Wilk test was used to assess data normality. Normally distributed data were assessed using one-way analysis of variance (ANOVA) and least significant difference (LSD) post hoc test for pairwise comparisons was performed to evaluate significant differences within or among groups. Non-normally distributed data were calculated using the Kruskal–Wallis test and Dunn-Bonferroni post hoc test was conducted. Categorical data were analyzed by $\chi 2$ test or Fisher's exact test. $P < 0.05$ was deemed to be statistically significant.

Probit regression was used to perform dose-response analysis. The primary endpoint was the effective rates of labor analgesia for different doses of dexmedetomidine with 0.075% ropivacaine at 30-minutes of epidural drug injection. An effective dose was defined as NRS pain score ≤ 3 at 30-minutes of epidural drug injection. ED_{50} and ED_{95} values for epidural dexmedetomidine combined with 0.075% ropivacaine with 95% CIs were derived by interpolation.

Results

Parturient recruitment is shown in Figure 1. 142 parturients were assessed for eligibility. Finally, a total of 120 parturients were randomized, allocated, received, and included in the data analysis. There were no statistically differences in cervical dilation before epidural drug injection, maternal age, height, weight, parity, proportion of nulliparous parturients and gestational age among groups (Table 1).

The dose-response relationship of dexmedetomidine with ropivacaine for epidural labor analgesia were performed using probit regression. The probit regression curve is shown in Figure 2. The estimated values of ED_{50} and ED_{95} with 95% CIs for epidural dexmedetomidine combined with 0.075% ropivacaine were 0.085 (0.015 to 0.133) μg/mL and 0.357 (0.287 to 0.493) μg/mL, respectively.

According to our definition, there were 12, 11, 6, 2, 0 and 0 patients with inadequate analgesia in the 0-, 0.1-, 0.2-, 0.3-, 0.4- and 0.5-μg/mL groups (20 cases per group), respectively. Epidural labor analgesia was effective in 40, 45, 70, 90, 100 and 100% of the 0-, 0.1-, 0.2-, 0.3-, 0.4- and 0.5-μg/mL groups, respectively. No differences were found among groups for sensory block level, number of parturients with Bromage score > 0, total dosage of analgesics, cesarean delivery rate, fetal birth weight, Apgar score at 1-minute and Apgar score at 5-minutes. Compared with other groups, Group Dexmedetomidine 0.5 μg/mL had a longer duration of the first stage of labor ($P < 0.05$) (Table 2).

No statistical differences were noted for adverse effects including hypotension, nausea and vomiting, pruritus, bradycardia, maternal fever, respiratory depression, and excessive sedation (Table 3).

Discussion

In this study, we have derived the dose-response curve for dexmedetomidine with ropivacaine given epidurally for labor analgesia. The values of ED_{50} and ED_{95} with 95% CIs for epidural dexmedetomidine with 0.075% ropivacaine for labor analgesia, in the setting of the conditions of the present study, were 0.085 (0.015 to 0.133) and 0.357 (0.287 to 0.493) μg/mL, respectively.

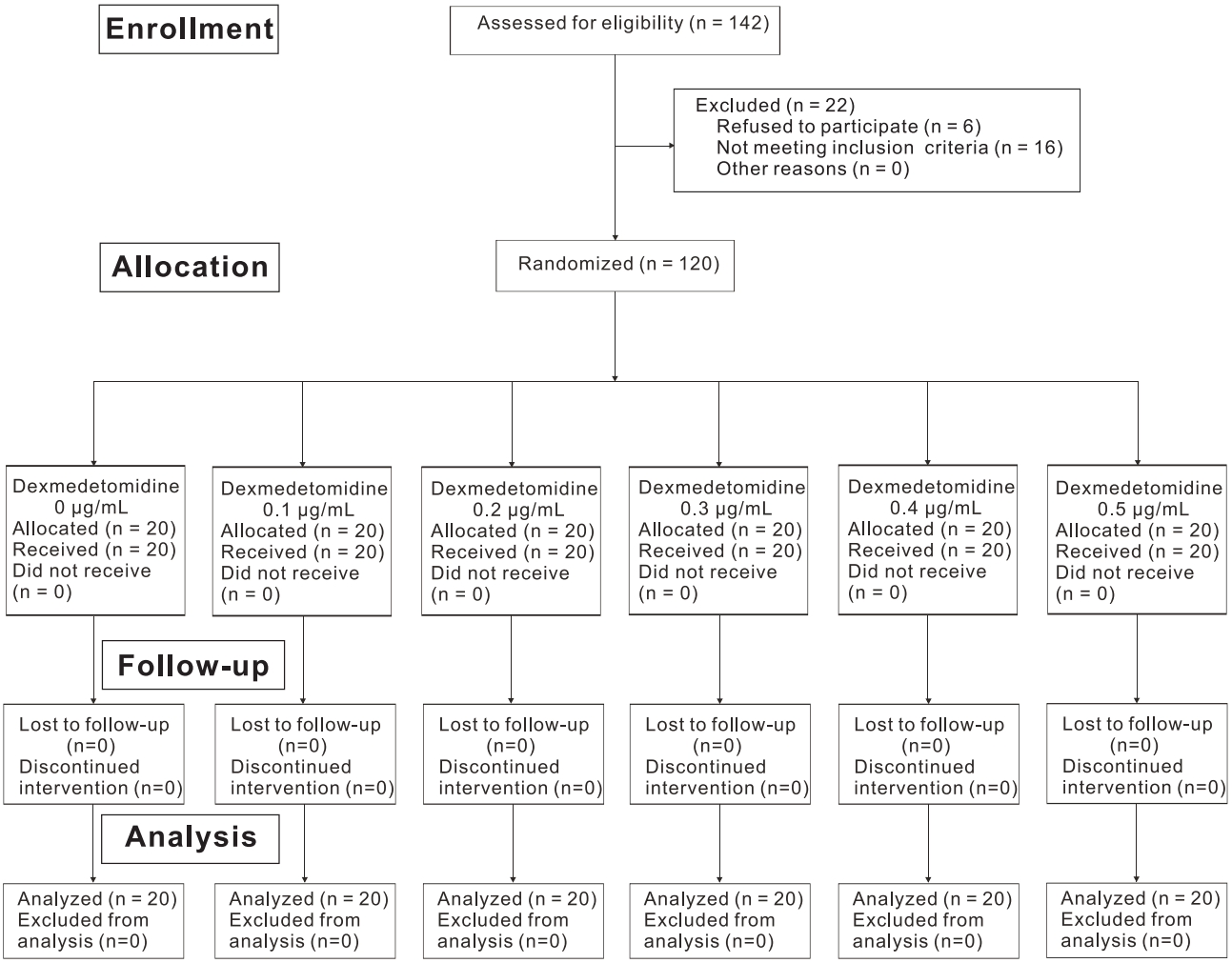

Figure 1 CONSORT showing flow of laboring parturients.

Previously, there is uncertainty regarding the optimal dose of epidural dexmedetomidine for labor analgesia, with doses ranging from 0.4 to 0.5 μg/mL published in the articles.[13,14] One earlier study showed that when comparing four different doses (0.25, 0.5, 0.75, and 1 μg/mL), the optimal dose of epidural dexmedetomidine was 0.5 μg/mL. However, we found that 0.5 μg/mL dexmedetomidine for epidural labor analgesia will prolong the labor process.[13] In another study, it has been reported that 0.4 μg/mL dexmedetomidine was the lowest concentration for optimal clinical efficacy in 5 different doses of dexmedetomidine (0, 0.3, 0.4, 0.5 and 0.6 μg/mL).[14] It is obvious that their optimal dose of epidural dexmedetomidine is only the best dose between groups, not the best dose at the lowest concentration.

Our optimal dose (ED_{95}) was lower than those reported in literatures of "minidose" epidural dexmedetomidine for labor analgesia.[13,14] The ED_{95} of epidural dexmedetomidine for labor analgesia was 0.357 μg/mL. To the best of our knowledge, this study was the first to use probit regression to illuminate an analgesic dose-response relationship for epidural dexmedetomidine combined with ropivacaine for labor analgesia, and a more accurate ED_{95} value for epidural dexmedetomidine was calculated.

Our findings are consistent with previous studies showing dexmedetomidine can be safely and effectively used for epidural labor analgesia.[6–12] Opioids are the most common epidural adjuvants for labor analgesia.[1–3] However, opioids can lead to dose-related adverse effects such as nausea, vomiting and pruritus.[4,5] Dexmedetomidine can effectively enhance epidural labor analgesia by taking effect on α-2 receptors in the spinal dorsal horn and decrease the incidence of opioid-related adverse effects.[6,8,9,16] It has been reported that dexmedetomidine has better analgesic effect than sufentanil in the first labor process and analgesic effect.[9,17] A low dose dexmedetomidine (≤ 0.5 μg/mL) resulted in

Table 1 Demographic Data

	Dexmedetomidine 0 μg/mL (n = 20)	Dexmedetomidine 0.1 μg/mL (n = 20)	Dexmedetomidine 0.2 μg/mL (n = 20)	Dexmedetomidine 0.3 μg/mL (n = 20)	Dexmedetomidine 0.4 μg/mL (n = 20)	Dexmedetomidine 0.5 μg/mL (n = 20)	*P* value
Age (years)	27.9 ± 2.7	28.3 ± 4.1	27.9 ± 3.2	27.9 ± 2.3	28.0 ± 3.5	28.3 ± 3.5	0.996
Height (cm)	161.7 ± 4.4	160.5 ± 4.1	160.6 ± 5.3	161.7 ± 4.2	159.0 ± 3.8	161.1 ± 4.2	0.401
Weight (kg)	70.3 ± 5.6	66.6 ± 10.7	69.4 ± 11.7	70.4 ± 7.7	67.2 ± 6.1	67.9 ± 7.6	0.607
Parity	0 (0–1)	0 (0–1)	0 (0–0)	0 (0–1)	0 (0–1)	0 (0–1)	0.986
Nulliparous	14 (70%)	14 (70%)	15 (75%)	14 (70%)	13 (65%)	13 (65%)	0.985
Gestational age (weeks)	39.2 ± 1.1	38.9 ± 1.0	38.9 ± 1.0	39.3 ± 0.8	38.9 ± 0.7	39.3 ± 0.9	0.423
Cervical dilation (cm)	2.8 ± 0.7	3.2 ± 0.6	2.8 ± 0.6	3.1 ± 0.4	3.1 ± 0.6	3.0 ± 0.6	0.157

Notes: Data are mean ± SD (standard deviation), or median (interquartile range) or number (%).

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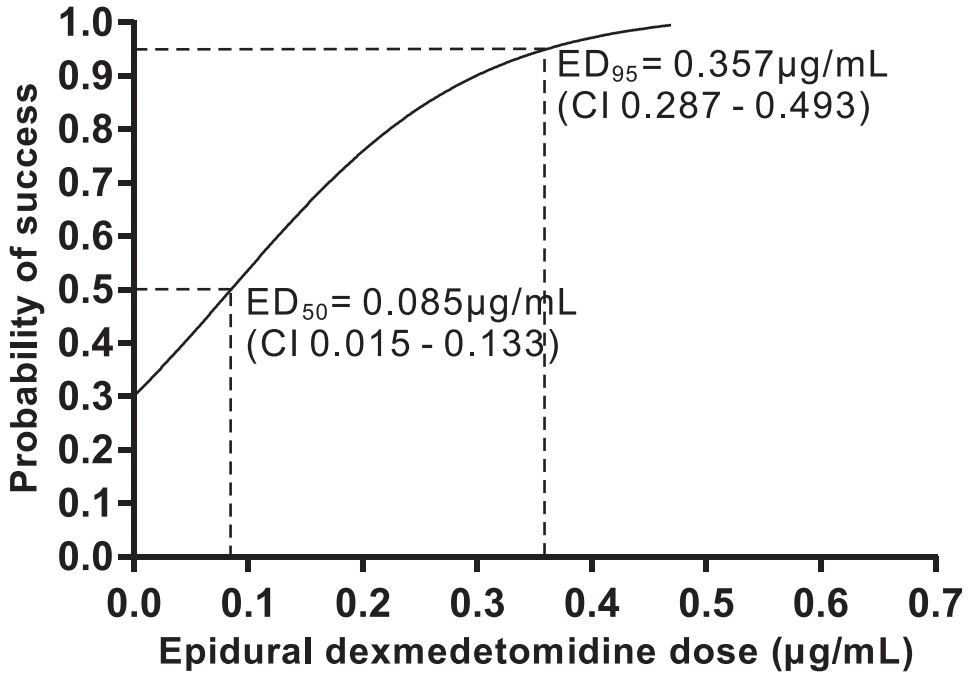

Figure 2 Dose-response curve for epidural dexmedetomidine (with 0.075% ropivacaine) for labor analgesia derived from probit analysis.

dose-sparing effects of local anesthetic, which may decrease the incidence of motor block and assisted vaginal delivery.[11,18] Our results also indicated that low-dose dexmedetomidine (≤ 0.5 μg/mL) was safe for epidural labor analgesia, as there were no significant differences in Apgar scores and adverse effects between the dexmedetomidine-free group and other groups.

In this study, ropivacaine was chosen for epidural labor analgesia because of its less neurotoxicity and cardiotoxicity. A number of animal experiments have confirmed that ropivacaine has less neurotoxicity and inhibitory effect on the heart than bupivacaine.[19,20] In addition, numerous published studies found that ropivacaine was safe and effective in a variety of clinical settings during epidural labor analgesia.[21,22]

Various epidural adjuvants have been routinely added to local anesthetics when used for labor analgesia. First, lipophilic opioids are widely used for epidural labor analgesia, which have synergistic and additive analgesic effects with local anesthetics, leading to the dose-sparing effect of local anesthetics.[1–3] Second, neostigmine has been administered epidurally with local anesthetics in the setting of labor analgesia. However, severe nausea and vomiting limit its use in obstetrics especially intrathecal administration.[23,24] Third, clonidine is a lipophilic α-2 receptors agonist to provide analgesia for parturients with opioid intolerance. However, large doses of clonidine may cause adverse effects such as maternal bradycardia and excessive sedation, which limits its popularization and application in clinic.[25–27] Fourth, pregabalin is also considered as epidural adjuvant for labor analgesia, showing that the regulation of emotional components of pain and visceral sensitivity is a new way for the treatment of labor pain.[28]

We also had some limitations. First, dexmedetomidine has not been consented by Food and Drug Administration (FDA) used as epidural adjuvant for labor analgesia, but numerous clinical studies have shown that epidural dexmedetomidine was safe and effective for labor analgesia. Second, we investigated the dose-response of dexmedetomidine combined with 0.075% ropivacaine, whereas the results may not be generalized to other concentrations of ropivacaine. Further trials are needed to explore this question. Third, we did not perform blood gas analysis on the umbilical cord because there was no blood gas analyzer in the delivery room. However, there were no significant differences in Apgar scores between the dexmedetomidine-free group and other groups, indicating there may be no significant differences in cord blood gas between groups. Forth, this was a single-center clinical trial, whereas the clinical promotion of dexmedetomidine needs a multi-center study.

Table 2 Labor Analgesia Characteristics and Neonatal Outcomes

	Dexmedetomidine 0 μg/mL (n = 20)	Dexmedetomidine 0.1 μg/mL (n = 20)	Dexmedetomidine 0.2 μg/mL (n = 20)	Dexmedetomidine 0.3 μg/mL (n = 20)	Dexmedetomidine 0.4 μg/mL (n = 20)	Dexmedetomidine 0.5 μg/mL (n = 20)	*P* value
Patients with inadequate analgesia	12	11	6	2	0	0	
Success rate	8 (40%)	9 (45%)	14 (70%)	18 (90%)	20 (100%)	20 (100%)	
Sensory block level	T8 (8–9)	T9 (7–10)	T8 (7–10)	T8 (7–8)	T8 (6–9)	T8 (7–8)	0.075
Bromage score > 0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000
Onset of analgesia (minutes)	14.1 ± 5.2	14.2 ± 2.5	15.4 ± 5.6	15.2 ± 3.5	16.7 ± 6.3	12.7 ± 4.4	0.186
Duration of first stage (minutes)	405.1 ± 147.9*	435.4 ± 280.3*	422.5 ± 204.0*	419.4 ± 200.8*	421.6 ± 195.1*	622.3 ± 333.0	< 0.05*
Duration of second stage (minutes)	58.6 ± 48.4	47.9 ± 41.1	57.7 ± 35.6	41.9 ± 31.9	46.9 ± 35.7	62.7 ± 42.5	0.535
Total dosage of analgesics (mL)	20.7 ± 10.7	23.5 ± 15.4	27.2 ± 19.1	25.8 ± 14.5	24.4 ± 14.9	32.0 ± 21.0	0.384
Cesarean delivery rate	0 (0%)	3 (15%)	0 (0%)	1 (5%)	0 (0%)	1 (5%)	0.131
Fetal birth weight (g)	3400.0 ± 282.0	3447.1 ± 403.3	3302.5 ± 396.2	3451.8 ± 329.9	3366.3 ± 371.0	3400.0 ± 308.6	0.865
Apgar score, 1 min	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	1.000
Apgar score, 5 min	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	10 (10–10)	1.000

Notes: Data are mean ± SD (standard deviation), or median (interquartile range) or number (%). *P < 0.05 for comparison with 0.5 μg/mL value using one-way analysis of variance (ANOVA) and least significant difference (LSD) post hoc test.

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Table 3 Adverse Effects

	Dexmedetomidine 0 μg/mL (n = 20)	Dexmedetomidine 0.1 μg/mL (n = 20)	Dexmedetomidine 0.2 μg/mL (n = 20)	Dexmedetomidine 0.3 μg/mL (n = 20)	Dexmedetomidine 0.4 μg/mL (n = 20)	Dexmedetomidine 0.5 μg/mL (n = 20)	*P* value
Hypotension	0	0	0	0	0	0	1.000
Nausea and vomiting	0	0	0	0	0	0	1.000
Pruritus	0	0	0	0	0	0	1.000
Bradycardia	0	0	0	0	0	0	1.000
Maternal fever	0	1	0	3	2	0	0.138
Respiratory depression	0	0	0	0	0	0	1.000
Excessive sedation	0	0	0	0	0	0	1.000

Note: Data are numbers.

Conclusion

In conclusion, under the conditions of this study, the ED_{50} and ED_{95} value of dexmedetomidine for epidural labor analgesia was 0.085 and 0.357 μg/mL. Dexmedetomidine is a suitable adjuvant for epidural labor analgesia.

Article Highlights

- The optimal dose of dexmedetomidine for epidural labor analgesia has not been fully determined.
- The dose-response relationship of dexmedetomidine for epidural labor analgesia was performed using probit regression.
- The ED_{50} and ED_{95} values of dexmedetomidine for epidural labor analgesia was 0.085 and 0.357 μg/mL under the conditions of this study.
- Dexmedetomidine is a suitable adjuvant for epidural labor analgesia.

Abbreviations

NRS pain scores, numerical rating scale pain scores; ED_{50}, the median effective dose; ED_{95}, the 95% effective dose; CIs, confidence intervals; ASA, American Society of Anesthesiologists; CRNA, certified registered nurse anesthesia; PCEA, patient controlled epidural analgesia; ANOVA, analysis of variance; FDA, Food and Drug Administration; CONSORT, Consolidated Standards of Reporting Trials.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was approved by the Ethical Committee of Affiliated Xiaoshan Hospital, Hangzhou Normal University (Hangzhou, China) and was registered at the Chinese Clinical Trials (Registration number: ChiCTR2000034367). All parturients provided written informed consent. We confirm our study complies with the Declaration of Helsinki.

Consent for Publication

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

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Disclosure

The authors declare no conflicts of interest in this work.

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