Drug Design, Development and Therapy

Dovepress
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CLINICAL TRIAL REPORT

Circadian Variation in Ropivacaine Requirement for Initiation of Epidural Labour Analgesia: A Random-Allocation Graded Dose-Response Study

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Purpose: There is evidence that labor pain and the doses of drugs used to treat it exhibit circadian variation. Previously, we reported that during the night, the effective dose (ED_{50}) of epidural ropivacaine for labor analgesia in 50% of patients was approximately 15% greater than that during the day. However, the influence of time of day on dose requirement at points higher on the dose-response curve is unknown. This double-blinded randomized trial aimed to determine and compare the full dose-response relationship for epidural ropivacaine administered to initiate labor analgesia during the day versus at night.

Patients and Methods: We recruited 150 nulliparous parturients requesting epidural labor analgesia during the day (day group, 07:01–19:00 h) and 150 during the night (night group, 19:01–07:00 h). Within each group, we randomly allocated patients to receive one of six doses of ropivacaine (7.5, 15, 22.5, 30, 37.5, or 45 mg) diluted to 20 mL to initiate epidural analgesia. Effective analgesia was defined as a visual analogue scale pain score of ≤ 3 cm (scale: 0–-10 cm) within 30 min. We generated dose-response curves for ropivacaine using probit regression and estimated the values for ED_{50} and ED_{95}.

Results: The estimated ED_{50} value of ropivacaine was greater during the night (22.4 [95% CI 19.9 to 24.8] mg) than during the day (17.9 [95% CI 15.7 to 20.0] mg), and the estimated ED_{95} value was greater during the night (41.3 [95% CI 36.4 to 48.7] mg) than during the day (32.9 [95% CI 28.9 to 39.0] mg).

Conclusion: The time of day is an important factor that should be considered when selecting the dose of ropivacaine to initiate epidural labor analgesia.

Trial Number and Registry Url: ChiCTR1900025381; https://www.chictr.org.cn/bin/project/edit?pid=42363.

Keywords: pain, labor, analgesia, epidural, anesthetics, local, ropivacaine, dose-response relationship, drug, chronobiology

Introduction

Labor pain perception exhibits circadian variation, with greater pain intensity during the night than during the day.[1,2] This can result in a difference in the dose requirement for drugs administered for epidural labor analgesia according to the time of day during which it is requested. In a previous study, in which we used an up-and-down methodology, we reported that the effective dose (ED_{50}) of ropivacaine administered for epidural labor analgesia in 50% of patients was approximately 15% greater during the night than during the day.[3] However, ED_{50} values do not necessarily represent doses that clinicians use in practice, and determination of the effect of time of day on the full dose-response curve for epidural ropivacaine likely has greater clinical relevance because most anesthetists prefer to administer doses greater than the ED_{50}, and differences in drug potency at higher points on the dose-response curve may not be the same as differences at the ED_{50} level.[4]

https://doi.org/10.2147/DDDT.S573078
Received: 25 October 2025
Accepted: 26 February 2026
Published: 10 March 2026

The aim of the present study was to determine and compare the full dose-response relationships for epidural ropivacaine administered to initiate labor analgesia during the day versus during the night using a traditional dose-response methodology. We used probit regression to generate full dose-response curves and to estimate values for ED_{50} and ED_{95} during the day and night.

Materials and Methods

Study Design

This was a prospective, double-blinded, two-arm parallel, random-allocation graded dose-response study. The study was approved by the Research Ethics Committee of Hangzhou Women's Hospital, Hangzhou, China (no. 201901-1) and all participants provided written informed consent to participate. This study was conducted in accordance with the principles of the Declaration of Helsinki. Prior to enrolling parturients, we registered this clinical trial with the Chinese Clinical Trial Registry (ChiCTR1900025381; https://www.chictr.org.cn/bin/project/edit?pid=42363).

We recruited 150 nulliparous parturients requesting epidural analgesia between 07:01- and 19:00 h (day group) and, during the same recruitment period, 150 equivalent patients during the 19:01- and 07:00 h (night group). Inclusion criteria were as follows: age 18–45 years, singleton gestation at 37–41 weeks, body mass index (BMI) $\leq$ 30 $kg.m^{-2}$, cervical dilation between 3–5 cm, and American Society of Anesthesiologists (ASA) physical status category II. Exclusion criteria were hypertension, diabetes, obstetric complications or suspected dystocia, allergy to local anesthetics, administration of opioid or sedative drugs in the preceding four hours, known fetal abnormalities, and any contra-indication to neuraxial anesthesia. Patients were instructed to use a 10-cm VAS (scale: 0–10 cm) to assess pain at the peak of uterine contractions.

Randomization and Blinding

We randomly allocated patients within each group to receive one of six different doses of epidural ropivacaine (7.5, 15, 22.5, 30, 37.5, or 45 mg). The ropivacaine doses were each diluted to a total volume of 20 mL using sterile normal saline and prepared in identical 20-mL syringes.

Randomization was stratified according to group and performed by an anesthesia assistant using codes generated with Microsoft Excel (Microsoft Corporation, Redmond, WA, USA). Codes were placed in sequentially labelled opaque envelopes, one of which was opened for each patient immediately after enrolment.

Anesthesia Procedure

Upon arrival in the labor room, all parturients received standard monitoring, including non-invasive blood pressure, pulse oximetry, electrocardiography, fetal heart rate, and tocodynamometry. Baseline measurements of blood pressure were recorded, an intravenous cannula was inserted, and 250 mL of warmed lactated Ringer's solution was infused.

Epidural analgesia was administered to the patient in the left lateral position. After skin disinfection and local anesthetic skin infiltration, the epidural space was located at the estimated L2-3 or L3-4 vertebral interspace with a 17-gauge epidural needle using the loss-of-resistance to saline technique (1–2 mL saline injected). Subsequently, with the orifice of the epidural needle facing cephalad, a wire-reinforced multi-hole catheter was inserted 4–5 cm into the epidural space. After gentle aspiration and checking for the presence of blood or cerebrospinal fluid, the catheter was secured to the patient's back using a transparent adhesive dressing and tape.

The study drugs were prepared using aseptic precautions by a dedicated assistant who had no further role in the study or clinical care of the patient.

An initial bolus of 5 mL of the study solution was administered as an epidural test dose, followed by a 1-mL saline flush. After confirming the absence of evidence of intrathecal or intravenous injection, the remaining 15 mL of the study drug was administered for approximately two minutes.

Pain scores were recorded at 5-min intervals at the peak of uterine contractions (primary outcome). Simultaneously, maternal blood pressure and heart rate were monitored along with the assessment of the fetal heart rate. The study period was defined as the time interval from administration of the initial dose to 30 min post-

dose. An effective response was defined as the achievement of a pain score ≤ 3 cm within the study period. Patients who achieved an effective response had analgesia maintained using ropivacaine 0.1% with sufentanil 0.33 μg/mL. Patients who did not achieve an effective response were administered an additional bolus of 10 mL of 0.2% ropivacaine. If the pain score remained > 3 cm at 15 min after the additional bolus, the epidural catheter was assumed to be non-functional; these patients were excluded from the analysis, their randomization code was reused for the next subsequent patient in that group, and further clinical management was at the discretion of the attending anesthetist.

Secondary study outcomes included sensory block level, motor block assessed using the modified Bromage scale, and side effects, including maternal hypotension (systolic blood pressure < 90 mmHg or < 80% of the baseline value), nausea, vomiting, shivering, pruritus, and fetal bradycardia. Hypotension was treated with intravenous boluses of 50 μg of phenylephrine. We also documented Apgar scores at 1 and 5 min after birth and umbilical arterial pH. The study also documented the incidence of induced labor.

Sample Size Calculation

The sample size was determined empirically based on a similar previously published dose-response study of epidural ropivacaine for labor analgesia.[4] The latter study included 15 patients in different epidural ropivacaine dose groups to determine the estimates of ED_{50} and ED_{95}. However, in that study, the 95% confidence intervals (CIs) for the estimates were wide; therefore, we arbitrarily increased the sample size in our study to 25 patients per dose subgroup to obtain more precise dose estimates.

Statistical Analysis

We used the Kolmogorov–Smirnov test to assess the distribution of data for normality. Variables with a normal distribution are presented as mean (SD) and were compared using the Student's *t*-test. Variables with non-normal distribution are presented as median (IQR) and were analyzed using the Mann–Whitney *U*-test. Categorical data are presented as numbers (%) and were analyzed using the chi-square or Fisher's exact test, as appropriate.

Dose-response data were analyzed using a probit analysis. In each of the two groups, the number of patients with a positive response in each dose subgroup was tallied and probit transformation was applied. Probit regression was then performed, and the values for ED_{50} and ED_{95} with 95% CIs were estimated by interpolation. The relative potency of ropivacaine was compared between groups by estimating the relative mean potency with 95% CIs. Response data for a full range of doses were obtained to generate sigmoidal dose-response curves.

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 22.0; IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 6.0; GraphPad Software, Inc., San Diego, CA, USA). Values of $p < 0.05$ (two-tailed) were considered statistically significant.

Results

The recruitment flow of patients is shown in Figure 1. Of the 312 parturients assessed for eligibility, 300 participants (150 in the day group and 150 in the night group) were recruited for the study and included in the final analysis. None of the patients were excluded because of inadequate analgesia after receiving the study dose and/or rescue bolus. The patient characteristics are presented in Table 1.

The number of patients who had a successful response in each dose subgroup in the two groups is shown in Table 2. From this data, a probit model was fitted with a Pearson goodness-of-fit chi-square p-value of 0.32, indicating that the model fitted the data well. The derived sigmoidal dose-response curves for epidural ropivacaine in the two groups are shown in Figure 2. The estimated values for ED_{50} were 17.9 (95% CI 15.7 to 20.0) mg in the day group and 22.4 (95% CI 19.9 to 24.8) mg in the night group. The estimated values for ED_{95} were 32.9 (95% CI 28.9 to 39.0) mg in the day group and 41.3 (95% CI 36.4 to 48.7) mg in the night group. The relative mean potency of ropivacaine in the night group versus the day group was 0.80 (95% CI 0.66 to 0.94). There was no difference in Apgar scores or umbilical arterial pH between groups.

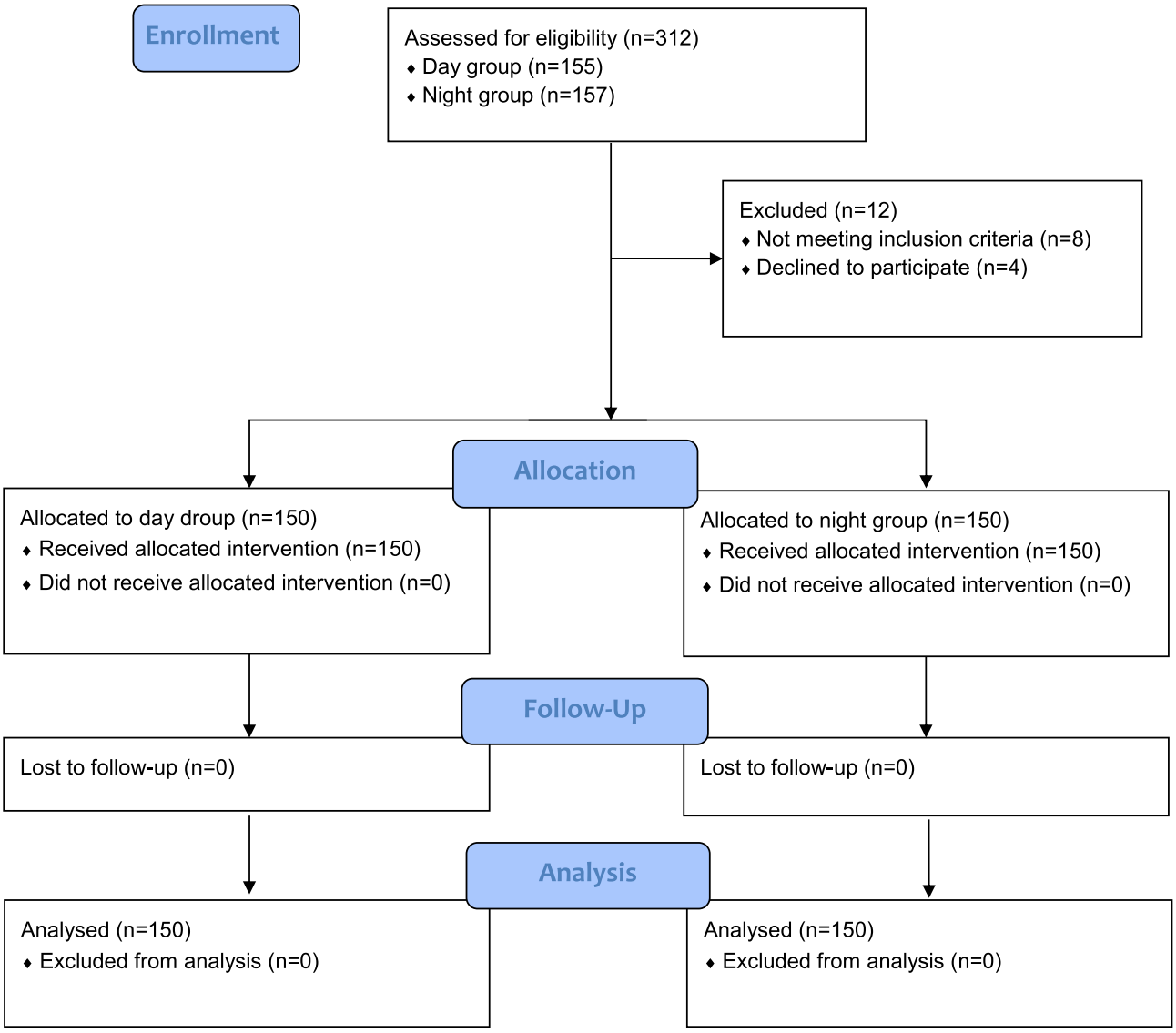

Figure 1 CONSORT diagram of patient recruitment.

Side effects during the induction period and neonatal outcomes were summarized in Table 3, and no significant differences were found in these parameters. In addition, there were no significant differences in anesthetic outcomes or the rate of induced labor between the two groups.

Table 1 Characteristics of Patients Receiving Epidural Analgesia During the Day or Night

	Day Group n = 150	Night Group n = 150
Age; y	28.5 (3.4)	28.3 (2.7)
Weight; kg	67.2 (7.3)	66.2 (6.5)
Height; cm	161.1 (4.7)	160.2 (4.6)
Cervical dilatation; cm	3.3 (0.6)	3.3 (0.5)
Gestational age; wk	39.1 (1.0)	39.0 (1.0)
Baseline visual analogue scale pain score; cm	7 [6–7]	7 [6–8]

Note: Values are mean (SD) or median [IQR].
Abbreviations: SD, standard deviation; IQR, interquartile range.

Table 2 Number of Patients with an Effective Response to Each of the Different Doses of Epidural Ropivacaine During the Day and During the Night. An Effective Response Was Defined as Achievement of a Visual Analogue Scale Pain Score ≤ 3 cm Within 30 minutes After Administration of Epidural Ropivacaine

Dose (mg)	Day Group n = 25	Night Group n = 25
7.5	0	0
15	8	2
22.5	19	15
30	23	21
37.5	24	24
45	25	22

Note: Data are represented as number.

Discussion

In this study, we determined full dose-response curves for ropivacaine for initiating epidural labor analgesia during the day and night. The main finding was that the dose-response curve during the night shifted significantly to the right compared with the day, indicating that when epidural labor analgesia is performed during the night, a greater dose of ropivacaine is required to produce effective analgesia compared with administration during the day. To quantify this difference, we estimated the relative mean potency (difference between ED_{50} values), which showed a difference of approximately 20% between night and day groups. Of clinical relevance, the differences between ED_{95} values were approximately the same.

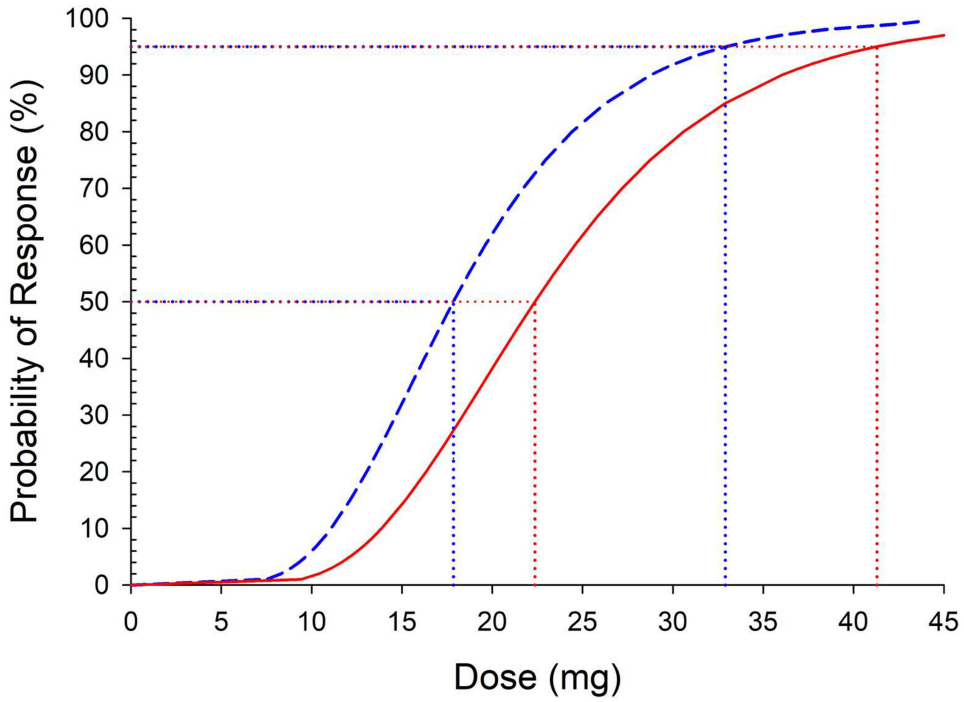

Figure 2 Dose-response curves for ropivacaine for initiating epidural analgesia during the day (dashed blue plot) and during the night (solid red plot). Dotted horizontal and vertical lines indicate the positions of ED_{50} and ED_{95}.

https://doi.org/10.2147/DDDT.S573078

Table 3 Side Effects During Induction Period and Neonatal Outcomes

	Day Group	Night Group	*P*
Maximum sensory level	T8 (T6, T10)	T8 (T7, T11)	0.198
Bromage Score (0/1/2/3)	149/1/0/0	150/0/0/0	>0.99
Maternal bradycardia	0 (0)	0 (0)	>0.99
Hypotension	8 (5.33)	8 (5.33)	>0.99
Nausea or vomiting	0 (0)	0 (0)	>0.99
Pruritus	0 (0)	0 (0)	>0.99
Shivering	1 (0.33)	0 (0)	>0.99
Fetal bradycardia	4 (2.66)	3 (2.00)	0.702
1-min Apgar	10 (10, 10)	10 (10, 10)	0.094
5-min Apgar	10 (10, 10)	10 (10, 10)	>0.99
Umbilical arterial pH	7.24 (7.21–7.32)	7.25 (7.23–7.27)	0.375
Induced labor	49 (32.67)	42 (28.00)	0.379

Notes: Data shown as number (%), or median (quartiles) as appropriate.

Various factors influence the efficacy of labor analgesia.[5] Although several previous studies have reported population-based estimates of dose requirements for local anesthetics for initiating labor analgesia,[4,6,7] we believe that for an individual patient, it is important to consider the clinical context and factors related to individual circumstances when selecting doses for initiating epidural labor analgesia. The results of our study suggest that the time of day (night vs day) is one of the factors that should be included in such considerations.

Previous studies have investigated the chronobiology of epidural labor analgesia. Earlier studies reported that the duration of epidural and intrathecal drugs administered for labor analgesia was shorter during the night than during the day[8–10] although this finding has not been consistent in all studies.[11] In our previous study,[3] rather than focusing on the duration of analgesia, we quantified the effect of the time of day by comparing epidural dose requirements. Similar to the results of the current study, we found that the dose requirement for epidural ropivacaine increased at night. However, in that study, we used an up-and-down methodology that only enabled estimation of the median effective dose. In the current study, we extended this work by determining full dose-response curves, which demonstrated that dose requirement was also increased at night at points higher than the dose-response curve, including ED_{95}. This is important because we believe that in typical clinical practice, it is likely that most anesthetists normally choose to administer doses closer to ED_{95} than ED_{50}.

Although the exact mechanism underlying the increased local anesthetic requirement for epidural labor analgesia at night is unknown, several factors may contribute to this. First, the neuroendocrine system exhibits circadian rhythms, including diurnal fluctuations in plasma concentrations of cortisol, adrenocorticotropic hormone, 5-hydroxytryptamine, endorphins, and oxytocin.[12,13] Elevated nocturnal levels of oxytocin and reduced nocturnal levels of beta-endorphin may lead to decreased pain tolerance in parturients and heightened pain sensitivity during late pregnancy.[13] Second, sleep disruption exacerbates pain sensitivity and induces nociceptive hypersensitivity,[14] and the onset of labor in pregnant women is accompanied by sleep deprivation and heightened fatigue, which negatively impacts the functioning of the opioid and 5-hydroxytryptamine systems, thereby exacerbating labor pain.[15,16] The experience of pain intensifies arousal, whereas sleep deprivation amplifies sensitivity to pain, resulting in a detrimental cycle that exacerbates both factors.[17] Third, variations in external environmental conditions between day and night may also contribute to the divergent pain perception experienced by patients.[18] For instance, during nocturnal hours, when the ambient environment is characterized by reduced noise levels, patients may allocate greater attention to monitoring contractions.

Our study had some limitations. First, the allocation of patients to the two groups was determined by the time of day, which was not randomized. However, patient recruitment for both groups was conducted during the same study period, and the allocation of doses within each group was randomized—neither the participants nor the anesthesiologists were aware of the ropivacaine dosage administered to each group—thereby substantially reducing potential bias and enhancing

internal validity. Second, the investigation was designed to investigate the dose-response relationship solely for ropivacaine. In clinical practice, it is common for clinicians to add lipophilic opioids, such as fentanyl or sufentanil, to the local anesthetic. Given that this study investigated primiparas with singleton only, the generizability of the results derived from this study was limited due to that multiparas may experience more tense labor pain. Finally, it remains to be determined whether the time of day has the same quantitative effect on the dose requirement of local anesthetic–opioid mixtures.

Conclusions

In summary, we have demonstrated a right shift in the dose-response curve for ropivacaine used to initiate epidural labor analgesia during the night compared to during the day. The dose requirement for ropivacaine was approximately 20% higher at night than during the day. These results suggest that the time of day is an important factor that should be considered when selecting local anesthetic doses for initiating epidural labor analgesia.

Abbreviation

ED_{95}, 95% effective dose.

Data Sharing Statement

Data related to this study can be obtained by contacting the corresponding author if reasonable.

Ethics Approval and Consent to Participate

The Ethical Committee of Hangzhou Women's Hospital approved this study and provided the certificate (no. 201901-1). All patients involved in this study were informed and all of them signed a written informed consent.

Funding

There is no funding to report.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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