BMC Anesthesiology

RESEARCH

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90% effective volume of 0.1% ropivacaine combined with 0.4 μg/ml sufentanil for epidural labour analgesia with push pump at a rate of 400 mL/hr and a bolus interval of 30 min: a double-blind sequential dose-finding study

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Abstract

Background It was reported that either shorter programmed intermittent epidural bolus (PIEB) intervals or high-speed bolus can produce more extensive epidural spread. We hypothesized that a combination of shortened time interval and increased speed of epidural bolus might further improve analgesic effect and therefore reduce the hourly volume for epidural labour analgesia.

Methods This double-blind dose-finding study used a biased coin up-and-down sequential allocation method to determine the 90% effective bolus volume of ropivacaine combined with sufentanil while using the push pump at a rate of 400 mL/hr and interval of 30 min to provide effective analgesia without breakthrough pain. We used 0.1% ropivacaine with 0.4 μg/mL sufentanil, with bolus volumes ranging from 3 to 6 mL. The first patient was assigned a volume of 3 mL, and the remaining volumes were assigned according to the biased coin-up-and-down method.

Results The estimated 90% effective volume (EV90) of ropivacaine combined with sufentanil for epidural labour analgesia at a time interval of 30 min was 4.88 mL (95% confidence interval 4.83–5.38).

Conclusions The optimum bolus volume of ropivacaine with sufentanil while using push pump at a time interval of 30 min is approximately 5 mL. It could probably further reduce the hourly bolus volume for epidural labour analgesia.

Keywords Labour Pain, Analgesia, Ropivacaine, Sufentanil

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Background

Programmed intermittent epidural bolus (PIEB) for labour analgesia provides similar or superior quality and longer duration of analgesia than those of continuous epidural infusions (CEI) [1–4]. However, there is no consensus on the current PIEB regimen. In a recent study using PIEB for labour analgesia, the researchers found that the distribution of the upper sensory levels to ice in their study appeared very similar to that obtained in their previous studies while using the same dose of bupivacaine but in a volume two times higher [4]. This finding suggests that single-dose volumes in PIEB do not have a significant effect on the upper sensory block. Recent studies have found that shorter PIEB intervals of 30–40 min may induce higher sensory block levels and better analgesic effect [4–7]. Oliver et al. also found in animal models that an infusion rate of 125 mL/hr produced less extensive epidural spread than 500 mL/hr [8]. This suggests that the increased speed of bolus delivery and shortened time interval together might be able to minimise the single bolus and further reduce the volume per hour, even throughout the labour course without affecting the analgesic effect.

We hypothesized that bolus volumes delivered with push pump at a rate of 400 mL/hr and an interval of 30 min would probably reduce the hourly volume for epidural labour analgesia.

Methods

Patient recruitment

This prospective, double-blind, sequential dose-finding study was approved by the China Ethics Committee of Registering Clinical Trials (ChiECRCT20200191). The study was registered prior to patient enrolment at http://www.chictr.org.cn (registration number: ChiCTR2000035465) on August 12, 2020. Written informed consent was obtained from all study participants after recruitment. The study was designed in accordance with the CONSORT reporting checklist.

Forty parturients were recruited from International Peace Maternity and Child Health Hospital between December 2021 and April 2022 who requested an epidural labour analgesia and met the following criteria: age 20 to 40 years, American Society of Anaesthesiologists (ASA) class II, full-term (> 37 weeks of gestation), singleton pregnancy, spontaneous or induced labour, normal foetal heart rate (FHR) and visual analogue scale (VAS) score ≥ 60 mm. The exclusion criteria were as follows: ASA class > II, any contraindications to epidural analgesia such as history of lumbar spine surgery, sepsis, coagulopathy or treatment with anticoagulants, allergy to opioids or local anaesthetics, multiparity, foetal distress or abnormalities, multiple gestations, body mass index above 36 kg/m^2, or parturient refusal.

Procedure of labour analgesia

All participants were recruited by W.M. and signed the informed consent form before the study. Subsequently, each parturient underwent a puncture on the left forearm using and 18-G catheter to establish intravenous access. Then 500 mL lactated Ringer's solution was quickly co-loaded (8 mL/kg/h) to prevent hypotension at the beginning of analgesia. Routine monitoring was performed and recorded every 5 min including non-invasive blood pressure, electrocardiography, pulse oximetry, heart rate, uterine activity, and foetal heart rate which was monitored by external tocodynamometry.

All epidural catheter insertion was performed by an experienced anaesthesiologist (J.Z.), with the parturient in the right lateral decubitus position. A 17-G Tuohy needle was used to perform epidural puncture using a paramedian approach at the anatomically determined L3–4 intervertebral interspace. The epidural space was identified by the loss of resistance to saline, and a single-orifice epidural catheter (Arrow FlexTip Plus epidural catheter set, Arrow International, Reading, Pennsylvania) was inserted into the epidural cavity for 5 cm through the Tuohy needle. Then the parturient was moved to a supine position with a pillow under the right hip, causing the left uterus to shift. Subsequently, a test dose of 3 mL 0.1% ropivacaine with 0.4 μg/mL sufentanil was administered to exclude the subarachnoid catheter insertion. After 3 min, a loading dose was administered consisting of two 6 mL boluses of 0.1% ropivacaine with 0.4 μg/mL sufentanil, given 3 min apart. To continue with the study, we required that a VAS score ≤ 30 mm was achieved within 20 min of administering the loading dose.

Subsequent boluses including 0.1% ropivacaine with 0.4 μg/mL sufentanil were delivered 45 min after the loading dose every 30 min. For all participants, a push pump (HP-30; Medcaptain Medical Co. Ltd, Suzhou, China) was used to deliver the boluses at a rate of 400 mL/hr. An unblinded research assistant (Y.S.) set up the epidural infusion pump. The epidural infusion pump was covered with an opaque bag to maintain blinding of the researchers, nurses, and parturients. Whenever the VAS scores were above 30 mm, the catheter slippage was ruled out first and then a patient-controlled epidural analgesia (PCEA) pump (MC ZZB-I; Apon Medical Tech. Co. Ltd, Jiangsu, China) with a PIEB mode was connected to the epidural catheter by J.Z. A bolus of 8 mL 0.1% ropivacaine with 0.4 μg/mL sufentanil for every 45 min was set and the first bolus was given through the PCEA pump for rescue. A 6-mL patient-controlled bolus dose with a 15-min lockout interval was also set and all parturients

were instructed to press the bolus button whenever their VAS scores were > 30 mm. The pump was stopped at the end of the third stage of labor.

Assessments included VAS scores, Modified Bromage scores, upper and lower sensory levels which were recorded by J.Z. for the first 20 min, and then hourly until 6 h after the epidural loading dose was administered or until the parturients cervix was fully dilated, whichever occurred first. The VAS score was used to evaluate pain, with 0 indicating no pain and 100 indicating the most severe pain imaginable. Modified Bromage scores (1, complete motor blockade; 2, almost complete motor blockade, with patient only able to move the feet; 3, partial motor blockade, with patient able to move the knees; 4, detectable weakness of hip flexion, with patient able to raise a leg but cannot keep it raised; 5, no detectable weakness of hip flexion, with patient able to raise a leg for ≥ 10 s; and 6, no weakness) were used to evaluate the degree of limb motor block after analgesia. The upper and lower sensory levels were tested using a cold sensation in an alcoholic cotton ball. Maternal bradycardia was defined as a heart rate < 50 beats/min and treated with atropine (0.5 mg). Foetal bradycardia was defined as an abrupt decrease in FHR > 15 beats/min below baseline for at least 60 s. If foetal bradycardia was detected, intrauterine resuscitation including maternal repositioning, an intravenous fluid bolus, oxygen administration was performed to ensure the safety of the foetus.

Immediately after delivery, all the observation data and 1 mL of umbilical arterial blood was collected by J.Z. and blood gas assessments were conducted using a blood gas analyser (iSTAT1 Analyzer MN:300-G, Abbott Point of Care Inc., Princeton, New, USA) with an iSTAT CG4 + test cartridge.

Biased- coin up-and-down (BCUD) design of the study

In this study, a bolus of 3 mL was used for the first parturient. The bolus for the subsequent parturient was increased or decreased by 0.5 mL, which was determined based on the response of the previous parturient. The bolus volume ranged from 2 to 6 mL, and the ceiling bolus volume was 6 mL. If VAS scores in the parturient were ≤ 30 mm and there were no requests for manual boluses until 6 h after the epidural loading dose was administered or until the cervix was fully dilated, whichever occurred first, the bolus used was considered a success. The next parturient was randomly assigned a bolus with a 1/9th chance of receiving a lower bolus (decreased by 0.5 mL), or an 8/9th chance of receiving the same bolus as that of the previous parturient. If the VAS score of the parturient was above 30 mm at any time 6 h after the epidural loading dose was administered, the bolus was considered a failure, and the bolus for the subsequent parturient was increased by 0.5 mL. The BCUD scheme prepared in Microsoft Excel 2016 (Microsoft Inc., Raymond, Washington, USA) was adopted by the research assistant (Y.S.) who was the only person with access to this software and knew the blous volume given to parturient.

Outcomes

The primary outcome was the effective volume by push pump that could successfully maintain VAS scores ≤ 30 mm with no requirement for manual boluses for 6 h after epidural analgesia initiation or until the maternal cervix was completely dilated, whichever came first.

The secondary outcomes were maternal and foetal observations. Maternal observations were as follows: Modified Bromage scores, upper and lower sensory level, use of oxytocin after analgesia, foetal bradycardia, pruritus, hypotension, bradycardia, nausea, vomiting, caesarean and forceps delivery, lateral episiotomy, total PCEA bolus times, duration of the three labour stages, duration of epidural analgesia, and postpartum haemorrhage. Neonatal observations included birth weight, Apgar scores measured 1 and 5 min after delivery, admission to the neonatal intensive care unit, and the pH of the umbilical arterial blood.

Maternal demographics before analgesia were also recorded, such as age, weight, height, gestational age, membrane rupture, oxytocin administration, cervical dilation, and VAS scores at request for analgesia.

Statistical analysis and sample size calculation

This dose-finding study, based on the BCUD design and simulation studies, suggests that the stopping rule of enrolling 20–40 patients will provide stable estimates of the target dose [10]. The sample size was 40 parturients in this study. The EV90 was defined as the volume that could achieve a successful analgesic effect in 90% of parturients and was estimated using the isotonic regression method [9, 10]. A statistician (T.X.) performed isotonic regression and bootstrapping using R version 3.4.4. software (R Foundation for Statistical Computing, Vienna, Austria) [11, 12]. Maternal characteristics and secondary outcomes are reported as mean ± standard deviation, numbers and proportions, and median (interquartile range) as appropriate. Statistical comparisons were made using SPSS version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Data on patient recruitment are shown in Fig. 1. Sixty parturients who underwent vaginal delivery and required epidural labour analgesia were recruited. Fifteen

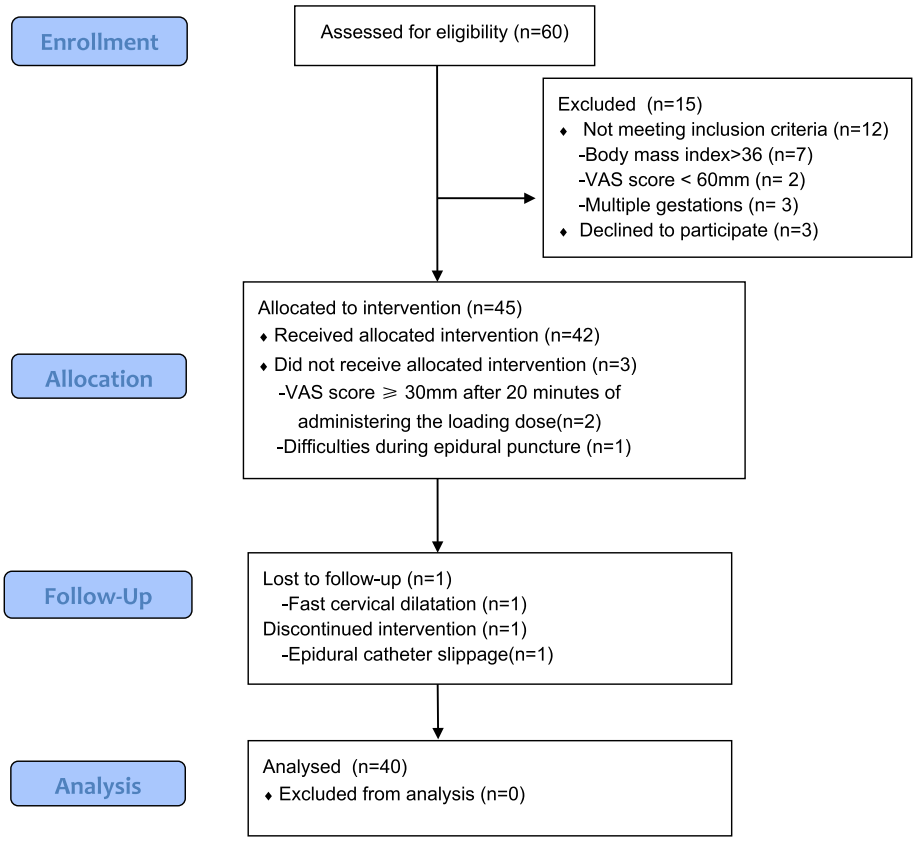

Fig. 1 Diagram of the study

parturients were excluded because of a higher body mass index ($n=7$), VAS score less than 60 mm ($n=2$), multiple gestations ($n=3$), or parturient refusal ($n=3$). One parturient had a difficult epidural puncture, and two had a VAS score ≥ 30 mm after 20 min of administering the loading dose. One parturient delivered within 1 h after epidural catheter placement and one had an epidural catheter slippage. After applying the inclusion and exclusion criteria, 40 patients were included in the final analyses. The maternal characteristics are listed in Table 1.

The sequence of effective and ineffective responses to each bolus volume of epidural administration for 40 successive parturients is shown in Fig. 2. The EV90 of ropivacaine combined with sufentanil for epidural labour analgesia at a bolus interval of 30 min was 4.88 mL (95% CI 4.83–5.38), which was determined using isotonic regression methods. The primary outcome was achieved in most parturients at a bolus of 5 mL; analgesia failed in 1 of the 21 parturients. Supplemental Table 1 gives the observed and PAVA-adjusted response rates for each bolus volume.

Table 2 presents the maternal outcomes. The occurrence rates were 2.5% for nausea and vomiting. No other adverse symptoms, such as hypotension, bradycardia, or pruritus were noted. The Modified Bromage scores in the parturients were 6. The incidence of oxytocin use after analgesia was 50%, caesarean delivery rate 7.5%, forceps delivery rate 5%, and lateral episiotomy rate 12.5%.

Table 1 Maternal characteristics of the 40 women enrolled in the study

Characteristics	Findings (N = 40)
Age (yr)	30.4 ± 3.5
Gestational age (weeks)	39.3 ± 1.0
Weight (kg)	70.0 ± 6.6
Height (cm)	161.9 ± 4.4
Membrane rapture	16 (40)
Oxytocin administration before analgesia	10 (25)
VAS at epidural analgesia request	90 (70–90)
Cervical dilation at onset of study	4 (3–4)

Values are mean ± SD, number (percentage), or median (IQR)

IQR interquartile range, *SD* standard deviation, *VAS* Visual Analog Scale

Table 3 presents the highest upper sensory level proportional distribution for each volume group. In group treated with 5 mL bolus, the highest upper sensory level of no less than T6 were achieved in 81% of parturients

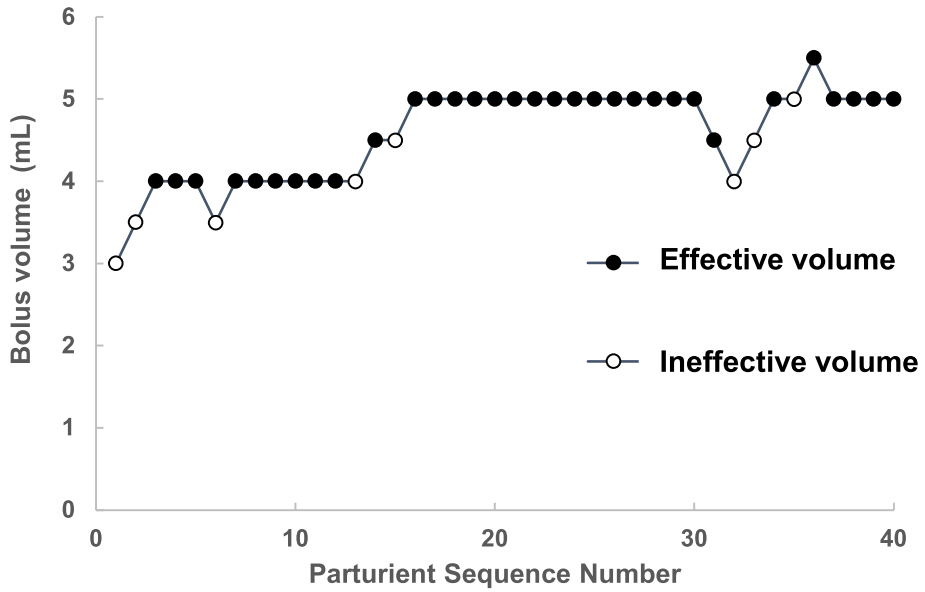

Fig. 2 The parturient allocation sequence and the response to the assigned bolus volume. The parturient's sequence number (X-axis) is the order of all parturients' exposures using biased coin up-and-down design. The assigned bolus volumes are displayed on the *y*-axis. An effective volume is denoted by a solid circle, while an ineffective volume is denoted by a hollow circle

Table 2 Maternal outcomes

Outcomes	Findings (N = 40)
Modified Bromage score	6 (6–6)
Upper sensory level	T6 (T6-T7.5)
Lower sensory level	S2 (S2-S2)
Oxytocin used after analgesia	20 (50)
Fetal bradycardia	1 (2.5)
Pruritus	0 (0)
Hypotension	0 (0)
Bradycardia	0 (0)
Nausea	1 (2.5)
Vomiting	1 (2.5)
Cesarean delivery	3 (7.5)
Forceps delivery	2 (5)
Lateral episiotomy	5 (12.5)
PCEA bolus times in failed cases	2 (1–3)
Total PCEA bolus times during 1st labor stage	0 (0–1)
Labor stage 1 (min)	468 ± 223
Labor stage 2 (min)	63 ± 53
Labor stage 3 (min)	9.2 ± 10.6
Duration of epidural analgesia (min)	355 ± 165
Postpartum hemorrhage (mL)	403 ± 100

Values are mean ± SD, number (percentage), or median (IQR)

SD standard deviation, *IQR* interquartile range, *PCEA* patient-controlled epidural analgesia

and no parturient had the highest upper sensory level above T4 or below T8.

Table 4 presents neonatal outcomes. Only two neonates had Apgar scores of 7 at 1 min, while the Apgar scores of remaining neonates were 10 at 5 min. The neonatal intensive care unit admission rate was 27.5%.

Discussion

Our study demonstrates that the optimum bolus of 4.88 mL 0.1% ropivacaine with 0.4 μg/mL sufentanil at a time interval of 30 min could provide effective analgesia in 90% of parturients while using the push pump at a rate of 400 mL/hr.

PIEB regimens used to be considered to produce better analgesia because of high-volume bolus which could improve spread of the local anaesthetic solution in the epidural space [13–16]. The bolus obtained in current study was a relatively small volume, it further supported the Bittencourt R et al.'s finding that small volume compared with large volume did not have a significant effect on the upper sensory block [4]. In their study on PIEB for labour analgesia, researchers attempted to reduce excessive sensory block levels by increasing the concentration of bupivacaine and reducing the single bolus volume in parturient women [4]. Although the study found no significant differences between this regimen and the original regimen in terms of total hourly local anaesthetic use and sensory block level, they emphasized that the distribution of the upper sensory levels to ice in their study seemed very similar to that obtained in their previous

Table 3 Highest upper sensory level in each subgroup

	PIEB bolus volume (mL)					
	3 (n = 1)	3.5 (n = 2)	4 (n = 11)	4.5 (n = 4)	5 (n = 21)	5.5 (n = 1)
Highest upper sensory level						
T4	0 (0.0)	0(0.0)	0(0.0)	0(0.0)	1(4.8)	0(0.0)
T5	0 (0.0)	0 (0.0)	3(27.3)	1(25.0)	7(33.3)	1(100.0)
T6	1 (100.0)	1(50.0)	5(45.4)	1(25.0)	9(42.9)	0(0.0)
T7	0 (0.0)	0 (0.0)	2(18.2)	1(25.0)	2(9.5)	0(0.0)
T8	0 (0.0)	1(50.0)	1(9.1)	1(25.0)	2(9.5)	0(0.0)

Data are presented as number (percentage)

Table 4 Neonatal outcomes

Outcomes	Findings (N = 40)
Birthweight (g)	3320 ± 363
Apgar scores at 1 min	10 (10–10)
Apgar scores at 5 min	10 (10–10)
1-Minute Apgar scores ≤ 7	2 (5)
Admission to NICU	11 (27.5)
UA blood pH	7.26 ± 0.07

Values are mean ± SD, number (percentage), or median (IQR)

SD standard deviation, *IQR* interquartile range, *NICU* neonatal intensive care unit, *UA* umbilical artery

studies while using the same dose of bupivacaine, but in a volume twice as high. This finding suggests that 10 mL and 5 mL single-dose volumes of PIEB do not have a significant effect on the upper sensory block. This leads us to believe that volume may not be the only determinant of drug distribution and that, time interval and speed of bolus infusion may be equally important for achieving the desired anaesthetic effect.

Previous studies have suggested that shorter PIEB intervals could induce higher sensory block levels [4–7]. Our study further shortened the interval to 30 min on the basis of their findings. The advantage of PIEB is that it allows for better drug distribution in the epidural space; however, patterns of drug administration at longer intervals result in a gradual loss of the upper sensory block after the drug effects achieve their peak, which causes fluctuations in drug effects. Although traditional CEI administration has a more stable effect, achieving the ideal sensory block level is difficult. The significance of our study is that when the PIEB interval was set at 30 min; not only we reduced the peak-trough fluctuation of the drug effect but also achieved the ideal sensory block level.

In previous studies, most PIEB regimens were administered with the traditional PIEB analgesia pump. In our study, we used the intermittent injection mode of the push pump to deliver epidural drugs at a rate of 400 mL/h instead of using the traditional PIEB analgesia pump. We chose the push pump because that the traditional PIEB analgesia pump cannot deliver drugs at speeds exceeding 300 mL/h [17–22]. Oliver et al. found in animal models that boluses administered with a high flow rate of 500 mL/h achieved a more extensive spread of local anaesthetic, which has not been confirmed in clinical trials that used flow rates of up to 300 mL/h [23, 24]. However, as Lange et al. pointed out, since there was a decrease in the median local anaesthetic consumption in the high-rate group, they could not entirely rule out differences in epidural distribution of local anaesthetic solution between the low and high-rate infusion groups [23]. Hence, the infusion speed of epidural boluses was set at 400 mL/h by push pump in current study for the purpose of a more extensive drug spread in epidural space.

Compared to previous studies that also aimed to reduce the hourly volume of analgesic solution [4–7], a shortened time interval of 30 min and increased speed of bolus infusion could slightly but further reduce the hourly volume of PIEB for epidural labour analgesia, which may have a positive and intended effect relative to the total labour course. After the epidural administration of the EV90 at an interval of 30 min, more than 81% of the mothers had upper sensory levels above T6, with a VAS score of less than 3 points until 6 h after the epidural loading dose was administered or until the woman's cervix was fully dilated, whichever occurred first. It is worth noting that none of the parturients in our study had injection difficulties, clogging, or other phenomena. Thus, another implication of the current study is that since the rate of 400 mL/h was well suited for epidural analgesia with no related adverse reactions, the conventional PIEB analgesia pump we currently use may no longer fully meet the clinical needs. Therefore, PIEB analgesia pump, which can provide higher delivery rate may be further developed.

Our study had some limitations. First, we studied only 30-min bolus volume intervals and did not evaluate other time intervals such as 45- or 15-min intervals. Second, our study used a single-orifice catheter; therefore, it is unknown whether using a multi-orifice catheter would need different delivery pressure and lead to a different blockade. Future studies should examine whether different delivery intervals, rates or epidural catheters would influence the results.

Conclusions

In conclusion, we found an intermittent bolus close to 5 ml with 0.1% ropivacaine and 0.4 μg/ml sufentanil delivered at a rate of 400 ml/h at a 30-min interval would probably reduce the hourly volume of PIEB for epidural labour analgesia. Further large-sample studies are expected to confirm its clinical efficacy.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02678-4.

Supplementary Material 1

Authors' contributions

Yuanqing Sun, MD helped with setting up the epidural infusion pump, data collection, drafting the manuscript, and final approval of the manuscript to be published. Wei Ma, MD helped with patient recruitment, drafting the manuscript and final approval of the manuscript to be published. Tao Xu, MD helped with conception and design of the study, statistics, revising the manuscript and final approval of the manuscript to be published. Jing Zheng, MD helped with conception and design of the study, data collection, anesthesia operation and interpretation, drafting the manuscript, critical revising the manuscript and final approval of the manuscript to be published.

Funding

None.

Availability of data and materials

The individual participant data that underlie the results reported in this article and study protocol, statistical anaylsis plan could be shared within 3 years following article publication with sound proposal. Proposals should be directed to Dr_anesCOCO@163.com.

Declarations

Ethics approval and consent to participate

This prospective, double-blind, sequential dose-finding study was approved by the China Ethics Committee of Registering Clinical Trials (ChiECRCT20200191). The study was registered prior to patient enrolment at www.chictr.org.cn (registration number: ChiCTR2000035465) on August 12, 2020. Written informed consent was obtained from all study participants after recruitment.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

Received: 4 December 2023 Accepted: 9 August 2024
Published online: 27 August 2024

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