ORIGINAL CLINICAL RESEARCH REPORT

OPEN

Randomized Assessment of the Optimal Time Interval Between Programmed Intermittent Epidural Boluses When Combined With the Dural Puncture Epidural Technique for Labor Analgesia

Han-Qing Yao, MD,* Jia-Yue Huang, MD,* Jia-Li Deng, MD,* Lin Liu, MD,* Ling Ai, MD,† Warwick D. Ngan Kee, MD, FANZCA, FHKCA,‡ and Fei Xiao, MD*

BACKGROUND: The dural puncture epidural (DPE) and programmed intermittent epidural bolus (PIEB) techniques are recent advances in neuraxial labor analgesia. Previous studies have investigated the PIEB optimal interval for effective analgesia when a standard epidural technique is used to initiate labor analgesia. However, it is unknown whether these findings are applicable when DPE is used.

METHODS: Patients were randomized into 1 of 5 groups with PIEB intervals of 35, 40, 45, 50, or 55 minutes. Labor analgesia was initiated on request with a DPE technique by epidural injection over 2 minutes of 15 mL of ropivacaine 0.1% with sufentanil 0.5 µg/mL after a dural puncture with a 25-gauge Whitacre needle. Effective analgesia was defined as no additional requirement for a patient-controlled bolus during the first stage of labor. The PIEB interval that was effective in 50% of patients (EI50) and 90% of patients (EI90) was estimated using probit regression.

RESULTS: One hundred laboring parturients received the DPE technique of whom 93 proceeded to have analgesia maintained with PIEB using 10 mL boluses of ropivacaine 0.1% and sufentanil 0.5 µg/mL. Totals of 89.5% (17/19), 84.2% (16/19), 82.4% (14/17), 52.6% (11/19), and 36.8% (7/19) of patients in groups 35, 40, 45, 50, and 55, respectively, received effective PIEB analgesia. The estimated values for EI50 and EI90 were 52.5 (95% CI, 48.4–62.6) minutes and 37.0 (95% CI, 28.4–40.9) minutes, respectively.

CONCLUSION: The estimate of the PIEB optimal interval for effective analgesia after the DPE technique was comparable to that reported in previous studies when analgesia was initiated using a conventional epidural technique. (Anesth Analg 2023;136:532–9)

KEY POINTS

- **Question:** What is the optimal interval between programmed intermittent epidural boluses for effective labor analgesia initiated using the dural puncture epidural technique for labor analgesia?
- **Findings:** The estimated values for optimal interval for effective analgesia in 50% (EI50) and 90% (EI90) of patients were 52.5 (95% CI, 48.4–62.6) minutes and 37.0 (95% CI, 28.4–40.9) minutes, respectively.
- **Meaning:** The programmed intermittent epidural bolus (PIEB) optimal interval for effective analgesia after the dural puncture epidural (DPE) technique is similar to previous estimates found when analgesia was initiated using conventional epidural analgesia.

GLOSSARY

ASD = absolute standardized difference; **BMI** = body mass index; **ChiCTR** = Chinese Clinical Trial Registration; **CI** = confidence interval; **CONSORT** = Consolidated Standards of Reporting Trials;

From the Departments of *Anesthesia and †Obstetrics, Jiaxing University Affiliated Women and Children Hospital, Jiaxing Maternity and Child Care Hospital, Jiaxing, China; and ‡Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Shatin, Hong Kong, China.

Accepted for publication June 20, 2022.

Funding: Research Fund for Lin He Academician New Medicine (19331208).

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

DOI: 10.1213/ANE.0000000000006201

Clinical Trials Registration: Chinese Clinical Trial Registration number: ChiCTR2100047291. URL: https://www.chictr.org.cn/showprojen.aspx?proj=126023.

Address correspondence to Fei Xiao, MD, Department of Anesthesia, Jiaxing University Affiliated Women and Children Hospital, Jiaxing Maternity and Child Care Hospital, East Zhonghuang Rd 2468, Jiaxing, Zhejiang 314050, China. Address e-mail to 13706597501@163.com.

CSF = cerebrospinal fluid; **DPE** = dural puncture epidural; **EI50** = effective interval of PIEB in 50% of patients; **EI90** = effective interval of PIEB in 90% of patients; **HR** = heart rate; **IRB** = Institutional Review Board; **PCEA** = patient-controlled epidural analgesia; **PIEB** = programmed intermittent epidural bolus; **SBP** = systolic pressure; **SD** = standard deviation; **VAS** = visual analogue scale.

The dural puncture epidural (DPE) and programmed intermittent epidural bolus (PIEB) techniques are recent advances in neuraxial labor analgesia.[1–10] Previous studies have investigated the optimal interval for effective analgesia between fixed-volume boluses of local anesthetic and lipophilic opioid during PIEB following initiation of analgesia using conventional epidural analgesia and have provided recommendations for clinical use.[11,12] However, whether these recommendations for the epidural technique are applicable to the DPE technique, which offers a conduit for medication translocation from the epidural to subarachnoid spaces, is unknown.[4] Accordingly, we hypothesized that the optimal PIEB interval for effective analgesia following initiation of analgesia with the DPE technique would be different than that following a conventional epidural technique. Therefore, we designed this study to investigate the optimal time interval for effective analgesia with PIEB using fixed volumes of 10 mL of ropivacaine 0.1% and sufentanil 0.5 µg/mL following initiation of labor analgesia using the DPE technique.

METHODS

This randomized, double-blinded study was approved by the Jiaxing University Affiliated Women and Children Hospital's institutional review board (IRB 2021–2023), and written informed consent was obtained from all subjects participating in the trial. The trial was registered before patient enrollment at http://www.chictr.org.cn/hvshowproject.aspx?id=137661 (Chinese Clinical Trial Registration [ChiCTR] 2100047291, principal investigator: H. Q. Yao, date of registration: June 11, 2021).

Inclusion criteria were: nulliparous singleton pregnancy, gestational age ≥37 weeks, American Society of Anesthesiologists Physical Status II, spontaneous onset of labor, latent phase of labor with cervical dilation 2 to 5 cm, and requesting neuraxial analgesia for painful uterine contractions. Exclusion criteria were: preeclampsia or hypertension, preexisting or gestational diabetes, body mass index (BMI) >35 kg/m^2, any contraindication to regional anesthesia, allergy or hypersensitivity to ropivacaine or sufentanil, and administration of opioids or sedatives within 4 hours preceding the request for neuraxial analgesia.

Routine monitoring included noninvasive blood pressure, pulse oximetry, electrocardiography (including respiratory rate monitoring), and fetal heart rate (HR). Baseline systolic pressure (SBP) and HR, defined as the mean of three readings between uterine contraction intervals, were recorded. Before the initiation of analgesia, an infusion of 250 mL of lactated Ringer's solution was commenced via an 18-gauge intravenous catheter placed in the upper limb.

Neuraxial analgesia using the DPE technique was initiated with patients in the left lateral position by 1 of 4 attending anesthesiologists. The L3-4 vertebral interspace was identified by ultrasound assessment. The epidural space was located with an 18-gauge Tuohy needle using the loss-of-resistance technique with <2 mL saline injected. A 25-gauge Whitacre needle was then inserted through the Tuohy needle to create a single dural hole, confirmed by clear flow of cerebrospinal fluid (CSF). The Whitacre needle was then removed without injection of any solution intrathecally. A 19-gauge multiport wire-reinforced flexible epidural catheter was then inserted 4–5 cm into the epidural space. After a gentle aspiration test was negative for CSF, a test dose of 3 mL of lidocaine 1.5% with epinephrine 15 µg was injected through the catheter. After confirmation of no signs of subarachnoid or intravenous injection were detected after 5 minutes, 15 mL of ropivacaine 0.1% with sufentanil 0.5 µg/mL was injected epidurally over 2 minutes to initiate labor analgesia. Patients were eligible to continue in the study if a visual analog scale[13] (VAS) pain score recorded after a contraction <1 (where 0 = no pain and 10 = worst pain imaginable) was achieved within 20 minutes after the epidural bolus.

Further analgesia was provided using PIEB with ropivacaine 0.1% and sufentanil 0.5 µg/mL delivered by an infusion pump (Apon MC ZZB-IV, Jiangsu Apon Medical Technology Co, Ltd) with an infusion rate of 500 mL/h. Patients were randomly allocated to 1 of 5 different PIEB intervals: 35 minutes (group 35), 40 minutes (group 40), 45 minutes (group 45), 50 minutes (group 50), and 55 minutes (group 55). These solutions were prepared in advance under sterile conditions by an anesthesia assistant. The randomization scheme was prepared by an investigator (F.X.), who was not involved in patients' pain management and data collection, in advance of patient enrollment using Microsoft Excel (Microsoft Corporation). The randomized scheme was kept in sequentially numbered opaque envelopes of which one was opened for each patient enrolled. All infusion pumps were set up by an unblinded research assistant. Blinding of investigators other than F. Xiao, midwives, and patients was achieved by covering the screen of the infusion device with opaque tape. The PIEB dose was fixed at 10 mL

with the first bolus given 1 hour after the initial manual loading dose with subsequent boluses continued at intervals according to patient group allocation. Any patient who requested further analgesia before the first PIEB bolus was excluded from the study. Supplemental analgesia was provided as required via patient-controlled epidural analgesia (PCEA) boluses of 8 mL with a 20-minute lockout interval and maximum dose of 30 mL/h. Patients were instructed to press the PCEA button whenever they subjectively considered they required further pain relief. If a patient made a PCEA request, the PIEB regimen was regarded as ineffective.

Pain scores (VAS) and characteristics of epidural block were checked 20 and 60 minutes after the loading dose bolus and then at 1-hour intervals until the patient's cervix was fully dilated when the study was terminated. Sensory block level was measured by assessing ability to discriminate cold sensation using alcohol wipes, and motor block was measured using the Bromage scale (0 = ability to move all joints in the leg, 1 = able to bend the knees and ankles, 2 = only able to move the ankle, and 3 = not able to move any leg joint). Hemodynamic parameters, including SBP and HR, were recorded at 20-minute intervals. If hypotension (defined as SBP < 90 mm Hg or <80% of baseline) occurred, the patient's position was changed to left lateral and the blood pressure was checked again. If hypotension persisted, ephedrine 5 mg was given intravenously and repeated as required. Fetal HR and uterine contractions were monitored using a fetal monitor (FM 20, Philips Medizin Systeme Boeblingen GmbH).

The research assistant checked the drug delivery system hourly. Consistent with previous studies,[11,12] the primary outcome of effective PIEB analgesia was defined as no requirement for PCEA during the first stage of labor. Patients who required PCEA were considered to have ineffective PIEB analgesia; for these patients, the study was terminated and further care was continued at the discretion of the attending staff. Secondary outcomes, including sensory block level, motor block, hypotension, maternal bradycardia (defined as HR < 60 beats/min), fetal bradycardia (defined as a fetal HR< 110 beats/min), and respiratory depression (defined as oxygen saturation < 90%), were recorded throughout the study period; and neonatal outcomes (neonatal weight, 1- and 5-minute Apgar scores, and umbilical arterial blood gases) were recorded after delivery. Patient satisfaction with labor analgesia was assessed after delivery using a verbal numerical ranking scale: 1 (not satisfied at all) to 5 (fully satisfied).

Statistical Analysis

Continuous variables were checked for normal distribution using graphical displays of the data and the Kolmogorov–Smirnov test. Demographic data were presented using descriptive statistics. In order to assess the degree of balance at baseline achieved in the randomization to the 5 time interval levels, the absolute standardized difference (ASD) between each of the pairs among the 5 levels was calculated for each parameter, and the maximum ASD among all pairs was identified. Imbalance was considered present when the maximum ASD was greater than the value calculated by the following equation, based on the recommendation for small sample sizes by Austin[14]:

$$\text{ASD} > 1.96 \times \sqrt{\left(\frac{(n1 + n2)}{n1n2}\right)}$$

where n1 and n2 are the per-group sample sizes for the pair. No adjustment was made to the analysis in the event that imbalance was detected.

Normally distributed data, including neonatal weight, umbilical arterial blood pH, and lactic acid concentration, are presented as mean (standard deviation [SD]). One-way analysis of variance was used to compare means among the groups, then pairwise group comparisons were made using post-hoc Bonferroni tests. Nonnormally distributed data including patient satisfaction and Apgar score are presented as median (quartiles). The Kruskal-Wallis test was used to compare the groups, and with post-hoc Dunn's tests for pairwise group comparisons. To test for trend in sensory level and patient satisfaction across the ordered randomized timing level groups, the Jonckheere-Terpstra test was applied. For categorical data including the incidence of side effects, the Cochran–Armitage χ^2 test for trend was used to test for linear trend in the parameter across the ordered randomized timing level groups. Time to patients' first request for additional analgesia by PCEA in each group was analyzed via Kaplan-Meier survival analysis with comparison between groups using the log-rank (Mantel-Cox) test. The effective interval of PIEB in 50% of patients (EI50) and 90% of patients (EI90) was estimated by probit regression. The Pearson goodness-of-fit χ^2 test was used to test the null hypothesis that the probit model adequately fitted the data. P values <.05 were regarded as statistically significant (two-sided). Where Bonferroni corrections were applied, adjusted P values were presented. Analyses were performed using IBM SPSS Statistics for Windows version 22.0 (IBM Corp), GraphPad Prism version 5.0 (GraphPad Software Inc), and Microsoft Excel (Microsoft Corporation).

Each of the 5 randomized timing intervals was described and analyzed as a group. Sample size was calculated using the Cochran-Armitage test using PASS (version 11.0.7; NCSS, LLC) based on the primary outcome of the study. According to a preceding

pilot study for the 5 groups with time intervals of 35, 40, 45, 50, and 55 minutes, the proportions of effective PIEB pain regimen were 90%, 80%, 75%, 50%, and 40%, respectively. Accordingly, we calculated that a sample size of 14 patients for each group (70 patients in total) was needed to have 90% power to detect a linear trend in the proportion of patients with an effective pain regimen among groups by using a Z test with continuity correction and a significance level of 0.05. To account for possible dropouts, the sample size was increased to 20 patients in each group.

RESULTS

Patient recruitment is shown in Figure 1. Of the initial 100 participants enrolled, 7 proceeded to cesarean delivery and were excluded. No patient requested further analgesia before the first PIEB bolus. Data from 93 participants were included in the final analysis (Figure 1). Patient demographic data are shown in Table 1. Assessment of ASD values suggested the presence of baseline imbalance for cervical dilation at request for epidural analgesia, and the duration of the first and second stages of labor.

Totals of 89.5% (17/19), 84.2% (16/19), 82.4% (14/17), 52.6% (11/19), and 36.8% (7/19) of patients in groups 35, 40, 45, 50, and 55, respectively, received effective PIEB analgesia. There was a significant linear trend across groups, $P < .001$. The time to patients' first request for additional analgesia by PCEA in each group is shown in Figure 2. The results of probit analysis are shown in Figure 3. Results of the Pearson goodness-of-fit χ^2 test indicated an adequate fit of the probit model ($P = .63$). The estimated values for EI50 and EI90 were 52.5 (95% CI, 48.4–62.6) minutes and 37.0 (95% CI, 28.4–40.9) minutes, respectively.

All patients developed a sensory block level above T10 after the initial dose. The highest sensory block level among groups (recorded at any time during the study period) is shown in Figure 4. There was a significant inverse linear trend between highest sensory level and PIEB time interval (Jonckheere-Terpstra test; $P < .001$). However, a low incidence of hypotension was observed among groups, and no patient required vasopressor therapy for hypotension. No patient developed a Bromage score >0 during the study. Side effects are shown in Table 2.

Neonatal outcome and patient satisfaction are presented in Table 2. There were no differences in neonatal weight, 1- and 5-minute Apgar scores, or umbilical arterial pH and lactic acid among groups.

Patient satisfaction was significantly different among groups (Table 2, $P = .001$). Post hoc testing showed that patient satisfaction was significantly lower in Group 55 compared with Group 35 (adjusted P value .003), Group 40 (adjusted P value .003), and Group 45 (adjusted P value .033). There was a significant inverse linear trend between patient satisfaction and the PIEB interval time (Jonckheere-Terpstra test, $P < .001$).

DISCUSSION

In this study, we found that following initiation of labor analgesia using the DPE technique, the effective interval values for PIEB in 50% of patients (EI50) and 90% of patients (EI90) were 52.5 (95% CI, 48.4–62.6) minutes and 37.0 (95% CI, 28.4–40.9) minutes, respectively.

The DPE and PIEB techniques are both recent advances that have been proposed to improve the quality of analgesia and patient satisfaction compared with traditional techniques of epidural labor analgesia. Use of the DPE technique has been shown to improve sacral spread, onset, and bilateral nature of epidural labor analgesia compared with traditional epidural analgesia, with a postulated mechanism of enhancing translocation of epidural medications through the dural puncture into the subarachnoid space.[4] Use of the PIEB technique has been shown to have the advantages of reducing the consumption of epidural local anesthetic, decreasing the degree of motor block and the incidence of breakthrough pain, and improving patient satisfaction compared with traditional epidural analgesia.[5–10] Recently, Song et al[15] reported that the combination of DPE and PIEB techniques was associated with faster onset of analgesia compared with conventional epidural analgesia and had a beneficial drug-sparing effect without increasing maternal or neonatal side effects compared with the combination of DPE technique and continuous epidural infusion. Although these results suggest that there may be benefits to the combination of the DPE and PIEB techniques, experience to date in this method remains limited. Our results provide further information regarding this combined technique although further research in this area is required to inform clinical practice.

The optimal interval for effective analgesia of PIEB for labor analgesia has been investigated in other recent studies. Epsztein Kanczuk et al[11] investigated PIEB using a fixed dose of 10 mL of bupivacaine 0.0625% and fentanyl 2 μg/mL. Using a biased-coin up-and-down sequential allocation method, they found that the EI90 was approximately 40 minutes. Using similar methodology, Zhou et al[12] found that the EI90 for PIEB using a fixed dose of 10 mL of ropivacaine 0.08% and sufentanil 0.3 μg/mL was about 42 minutes. Because our estimated value for EI90 (37.0 min [95% CI, 28.4–40.9]) was broadly similar to that reported in the previous studies, this suggests the possibility that initiation of labor analgesia using DPE technique rather than conventional epidural analgesia may not be a major factor influencing choice of

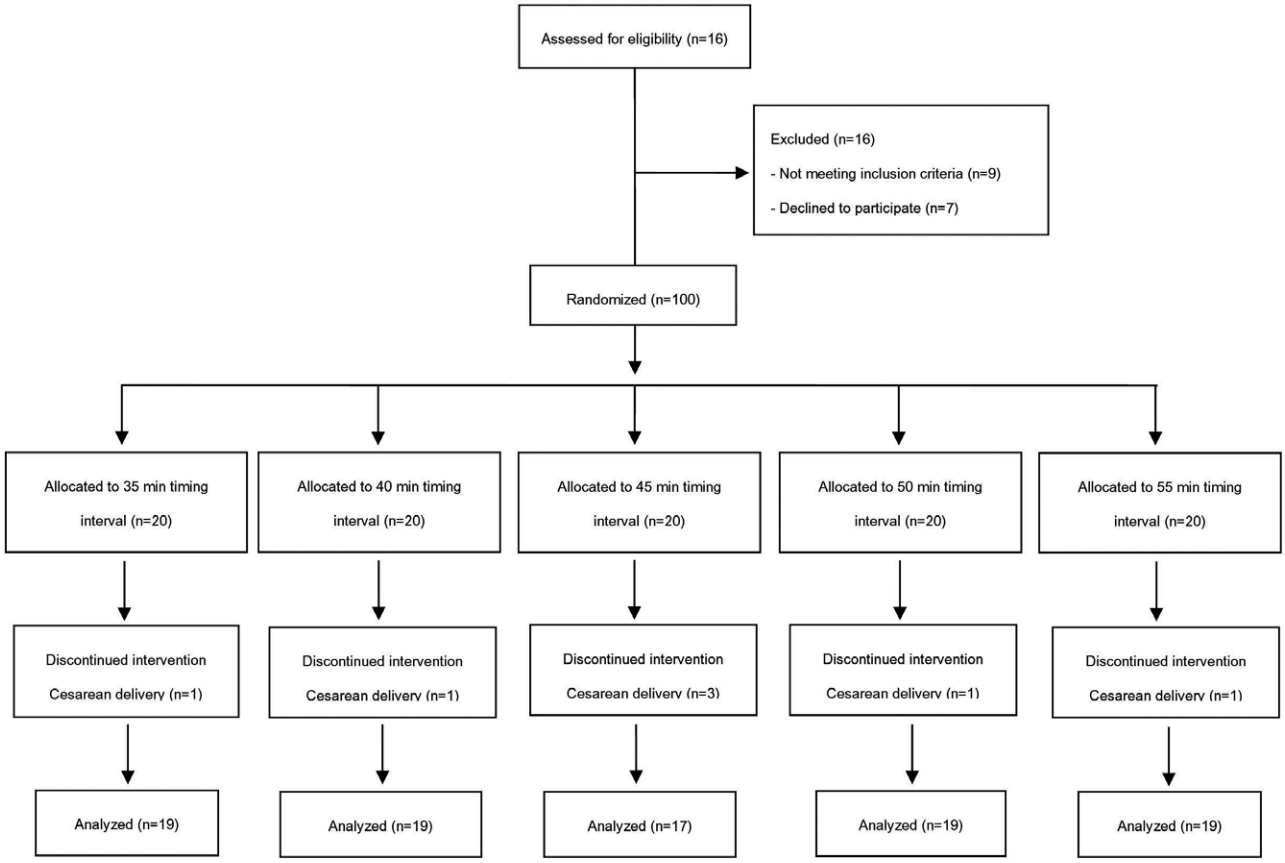

Figure 1. CONSORT flow diagram. CONSORT indicates Consolidated Standards of Reporting Trials.

Table 1. Demographics and Labor Characteristics

Characteristic	Randomized timing interval					Maximum absolute standardized difference between groups
	35 min (n = 19)	40 min (n = 19)	45 min (n = 17)	50 min (n = 19)	55 min (n = 19)	
Age, y	28.2 (2.7)	27.7 (4.5)	29.4 (3.7)	28.1 (4.2)	28.0 (4.7)	0.41 (0.65)
Body mass index, kg/m^2	26.0 (3.5)	27.4 (4.1)	26.6 (2.3)	26.6 (3.0)	27.7 (3.4)	0.47 (0.64)
Gestational age, wk	39.8 (1.0)	39.8 (1.1)	39.6 (1.2)	39.1 (2.4)	39.2 (1.2)	0.53 (0.64)
Pain score at request for epidural analgesia	7.1 (1.3)	7.5 (0.8)	7.8 (1.0)	7.4 (1.1)	7.8 (1.0)	0.46 (0.64)
Cervical dilation at request for epidural analgesia (cm)	2.1 (0.3)	2.2 (0.4)	2.4 (0.6)	2.1 (0.2)	2.2 (0.7)	0.66 (0.65)[a]
Duration of the first stage of labor (min)	480 (340–570)	320 (255–510)	303 (198.5–480)	430 (240–600)	360 (247–450)	0.75 (0.65)[a]
Duration of the second stage of labor (min)	49 (33–61)	30 (25–70)	38 (22.5–85)	35 (24–51)	40 (20–60)	0.75 (0.64)[a]

Data shown as mean (SD) and median (quartiles) as appropriate. Values shown for maximum absolute standardized difference between groups are the maximum values among all pairs of groups; the values in parentheses indicate the values, calculated from the data for the maximum-value pairs, above which imbalance among groups is likely present based on the recommendation by Austin.[14] Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples.

Abbreviation: SD, standard deviation.

[a]Baseline imbalance present.

Adapted from the work of Austin.[14]

PIEB regimen. However, we would caution that the epidural solution used in our study and in the previously reported studies differed, which limits the validity of comparisons. Therefore, we suggest that further research using a direct comparison is required to confirm whether the DPE technique is a major factor influencing choice of PIEB regimen.

In our study, we considered an optimal interval for PIEB to be the same as an effective interval. However, this can be debated. Previously, Epsztein Kanczuk et al[11] and Zhou et al[12] considered this in the context of PIEB when analgesia was initiated with a conventional epidural technique. They estimated intervals that produced effective analgesia as defined by no

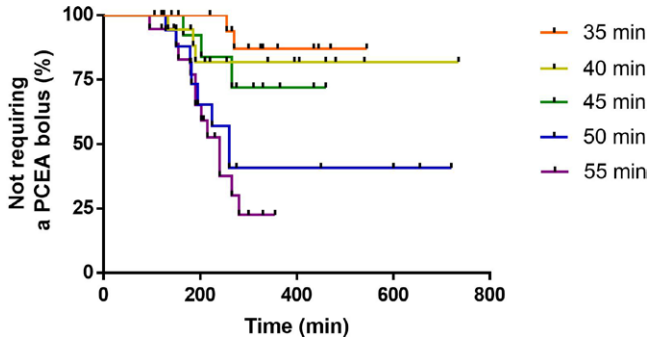

Figure 2. Kaplan-Meier survival curves presenting percentage of patients who did not require a PCEA bolus during the study period. There was a significant difference among groups (log-rank test; ***P*** = .0004). PCEA indicates patient-controlled epidural analgesia.

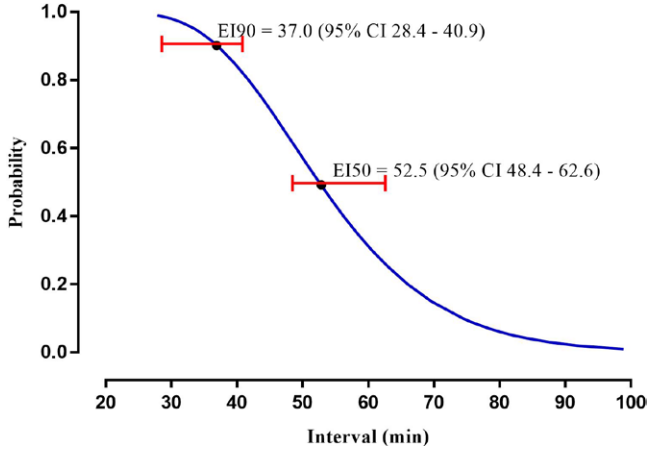

Figure 3. Interval time-response curve of ropivacaine 0.1% and sufentanil 0.5 µg/mL administered using the PIEB technique for maintaining labor analgesia after initiation of analgesia using the DPE technique. Data were analyzed using probit regression. The estimates for EI50 and EI90 were 52.5 (95% CI, 48.4–62.6) min and 37.0 (95% CI, 28.4–40.9) min, respectively. CI indicates confidence interval; DPE, dural puncture epidural; EI50, effective interval of PIEB in 50% of patients; EI90, effective interval of PIEB in 90% of patients; PIEB, programmed intermittent epidural bolus.

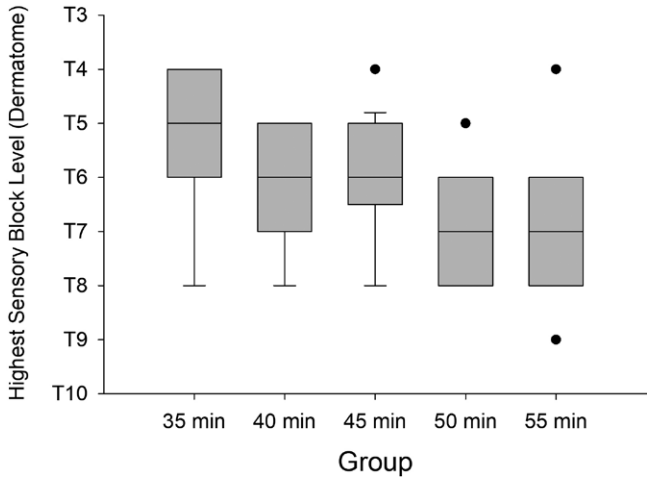

Figure 4. The highest sensory block levels for each group. Boxplots show median, 10th, 25th, 75th, and 90th percentiles and outliers. There was a significant difference among groups (Kruskal-Wallis test; ***P*** = .0002), and there was a significant inverse linear trend between highest sensory level and PIEB interval time (Jonckheere-Terpstra test; ***P*** < .001). PIEB indicates programmed intermittent epidural bolus.

need for a PCEA or manual supplemental epidural bolus (absence of breakthrough pain). An optimal interval was defined using EI90 as a reference target. However, it was noted that this definition is arguable as its use might result in excessive local anesthetic administration for some patients.[11] An associated potential for increased motor block and possible effect on the progress of labor would suggest that a PIEB interval aimed at 90% of patients not requiring supplemental analgesia may not necessarily be clinically

Table 2. Side Effects, Patient Satisfaction, and Neonatal Outcomes

	Randomized timing interval					
	35 min (n = 19)	40 min (n = 19)	45 min (n = 17)	50 min (n = 19)	55 min (n = 19)	*P* value
Hypotension	2 (11%)	1 (5%)	1 (6%)	0 (0%)	0 (0%)	.08[a]
Shivering	2 (11%)	2 (11%)	1 (6%)	2 (11%)	3 (16%)	.64[a]
Pruritus	5 (26%)	4 (21%)	5 (29%)	4 (21%)	5 (26%)	1.00[a]
Fetal bradycardia	1 (5%)	1 (5%)	1 (6%)	2 (11%)	2 (11%)	.41[a]
Patient satisfaction	5 (5–5)[b]	5 (5–5)[b]	5 (3–5)[b]	5 (4–5)	5 (3–5)	.0005[c]
Neonatal weight, g	3331 (448)	3353 (416)	3336 (361)	3361 (453)	3307 (428)	1.00[d]
1-min Apgar score	10 (10–10)	10 (9–10)	10 (10–10)	10 (10–10)	10 (9–10)	.50[c]
5-min Apgar score	10 (10–10)	10 (10–10)	10 (9–10)	10 (10–10)	10 (10–10)	.92[c]
Umbilical arterial pH	7.30 (0.07)	7.30 (0.09)	7.33 (0.09)	7.30 (0.05)	7.29 (0.06)	.62[d]
Lactic acid (mmol/L)	4.32 (1.29)	4.06 (0.92)	4.02 (1.46)	3.96 (1.26)	4.42 (1.25)	.74[d]

Data shown as number (%), median (quartiles), or mean (SD) as appropriate.

[a]Categorical data were analyzed using the Cochran-Armitage χ^2 test for trend.

[b]Ten post hoc pairwise comparisons were made using Dunn's test, and significant differences were found for groups 35, 40, and 45 compared with group 55, all adjusted $P < .05$.

[c]Nonnormally distributed data were analyzed using the Kruskal-Wallis test, and with Dunn's tests for post hoc pairwise comparisons if there was a significant difference among groups.

[d]Normally distributed data were analyzed using one-way analysis of variance.

ideal. In our study, we also estimated EI90. However, in contrast to the previous studies, we used random allocation dose-finding methodology to more fully define the relationship between dose interval and effective analgesia. We estimated values of EI50 as a conventional value and EI90 as a comparative value but our data could also be further analyzed to provide estimates of other values on the response curve, which might be more useful for individualized care. Of note, in our study, we found that decreasing PIEB interval was associated with higher sensory block levels, and in addition, 2 patients in group 35, 1 patient in group 40 and group 45, experienced hypotension. Conversely, patient satisfaction was greater as PIEB interval time decreased. These findings underline the importance of individualizing patient care.

Our study has some limitations. First, we investigated a PIEB bolus consisting of 10 mL of ropivacaine 0.1% and sufentanil 0.5 μg/mL. This solution is the standard epidural mixture in our clinical practice, and the 10 mL bolus size was chosen to be consistent with that used in other studies. It is possible that our findings may not be applicable to PIEB using different drug combinations or different bolus sizes. Second, the sample size in the current study was chosen to be sufficient to estimate the primary outcome of PIEB interval but may not be sufficient for some of the secondary outcomes for which the possibility of statistical error cannot be excluded. Third, we included only nulliparous patients in early labor. Our findings may not be generalizable to multiparous patients or those in more advanced labor. Fourth, the analysis showed the presence of baseline imbalance for cervical dilation at request for epidural analgesia, and duration of the first and second stages of labor. This potentially may have influenced the main findings although actual impact is difficult to identify. Finally, the study was terminated after patients' first PCEA request. Although this facilitated estimation of the primary outcome, the amount of information related to secondary outcomes such as sensory and motor blockade was limited.

In conclusion, in this study, we have investigated the relationship between time interval of PIEB when combined with the DPE technique and effectiveness of analgesia. Our estimated values for EI50 and EI90 may be useful to inform clinical practice. Further research using different drug mixtures and PIEB regimens is recommended.

ACKNOWLEDGMENTS

The authors thank all the staff at the Department of Laboring Room of Jiaxing University Affiliated Women and Children Hospital, Jiaxing, China, for their help in this study.

DISCLOSURES

Name: Han-Qing Yao, MD.
Contribution: This author helped with study design, study conduct, data analysis, and manuscript preparation.
Name: Jia-Yue Huang, MD.
Contribution: This author helped with study design, study conduct, data analysis, and manuscript preparation.
Name: Jia-Li Deng, MD.
Contribution: This author helped with study conduct and data collection.
Name: Lin Liu, MD.
Contribution: This author helped with randomization and data analysis.
Name: Ling Ai, MD.
Contribution: This author helped with study conduct and data collection.
Name: Warwick D. Ngan Kee, MD, FANZCA, FHKCA.
Name: Fei Xiao, MD.
Contribution: This author helped with study design, data analysis, and manuscript preparation.
This manuscript was handled by: Jill M. Mhyre, MD.

REFERENCES

1. Chau A, Bibbo C, Huang CC, et al. Dural puncture epidural technique improves labor analgesia quality with fewer side

effects compared with epidural and combined spinal epidural techniques: a randomized clinical trial. *Anesth Analg*. 2017;124:560–569.
2. Wilson SH, Wolf BJ, Bingham K, et al. Labor analgesia onset with dural puncture epidural versus traditional epidural using a 26-Gauge Whitacre needle and 0.125% bupivacaine bolus: a randomized clinical trial. *Anesth Analg*. 2018;126:545–551.
3. Gunaydin B, Erel S. How neuraxial labor analgesia differs by approach: dural puncture epidural as a novel option. *J Anesth*. 2019;33:125–130.
4. Cappiello E, O'Rourke N, Segal S, et al. A randomized trial of dural puncture epidural technique compared with the standard epidural technique for labor analgesia. *Anesth Analg*. 2008;107:1646–1651.
5. Capogna G, Camorcia M, Stirparo S, et al. Programmed intermittent epidural bolus versus continuous epidural infusion for labor analgesia: the effects on maternal motor function and labor outcome. A randomized double-blind study in nulliparous women. *Anesth Analg*. 2011;113:826–831.
6. Onuoha OC. Epidural analgesia for labor: continuous infusion versus programmed intermittent bolus. *Anesthesiol Clin*. 2017;35:1–14.
7. McKenzie CP, Cobb B, Riley ET, et al. Programmed intermittent epidural boluses for maintenance of labor analgesia: an impact study. *Int J Obstet Anesth*. 2016;26:32–38.
8. Holgado CM, Girones A, Tapia N, et al. Labor outcomes with epidural analgesia: an observational before-and-after cohort study comparing continuous infusion versus programmed intermittent bolus plus patient-controlled analgesia. *Minerva Anestesiol*. 2020;86:1277–1286.
9. Delgado C, Ciliberto C, Bollag L, et al. Continuous epidural infusion versus programmed intermittent epidural bolus for labor analgesia: optimal configuration of parameters to reduce physician-administered top-ups. *Curr Med Res Opin*. 2018;34:649–656.
10. Leone Roberti Maggiore U, Silanos R, Carlevaro S, et al. Programmed intermittent epidural bolus versus continuous epidural infusion for pain relief during termination of pregnancy: a prospective, double-blind, randomized trial. *Int J Obstet Anesth*. 2016;25:37–44.
11. Epsztein Kanczuk M, Barrett NM, Arzola C, et al. Programmed intermittent epidural bolus for labor analgesia during first stage of labor: a biased-coin up-and-down sequential allocation trial to determine the optimum interval time between boluses of a fixed volume of 10 mL of bupivacaine 0.0625% with fentanyl 2 µg/mL. *Anesth Analg*. 2017;124:537–541.
12. Zhou SQ, Wang J, Du WJ, et al. Optimum interval time of programmed intermittent epidural bolus of ropivacaine 0.08% with sufentanyl 0.3 µg/mL for labor analgesia: a biased-coin up-and-down sequential allocation trial. *Chin Med J (Engl)*. 2020;133:517–522.
13. Ngan Kee WD, Ng FF, Khaw KS, et al. Determination and comparison of graded dose-response curves for epidural bupivacaine and ropivacaine for analgesia in laboring nulliparous women. *Anesthesiology*. 2010;113:445–453.
14. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083–3107.
15. Song Y, Du W, Zhou S, et al. Effect of dural puncture epidural technique combined with programmed intermittent epidural bolus on labor analgesia onset and maintenance: a randomized controlled trial. *Anesth Analg*. 2021;132:971–978.