International Journal of Obstetric Anesthesia 51 (2022) 103571

Contents lists available at ScienceDirect

International Journal of Obstetric Anesthesia

journal homepage: www.elsevier.com/locate/ijoa

Original Article

The incidence of breakthrough pain associated with programmed intermittent bolus volumes for labor epidural analgesia: a randomized controlled trial

R.H. Zuo [a,b], J.J. Dang [a,b], J.W. Zhuang [a,b], Q.M. Chen [a,b], J.Y. Zhang [a,b], H.W. Zheng [a,b], Z.P. Wang [a,b,*]

[a] Key Laboratory of Anesthesiology, Xuzhou Medical University, Xuzhou, Jiangsu, China
[b] Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China

ARTICLE INFO

Keywords:
Breakthrough pain
Epidural analgesia
Labor
Prolonged second stage of labor

ABSTRACT

Background: In this randomized, blinded study, we evaluated the effects of different programmed intermittent epidural bolus (PIEB) volumes for labor analgesia on the incidence of breakthrough pain and other analgesic outcomes.

Methods: Nulliparous women with term cephalic singleton pregnancies who requested labor analgesia had epidural analgesia initiated with 10 mL 0.1% ropivacaine with sufentanil 0.3 μg/mL. The pump was programmed to deliver a 4, 6 or 8 mL bolus every 45 min (groups 4, 6 or 8, respectively). The primary outcome was the incidence of breakthrough pain, defined as inadequate analgesia after two patient-controlled epidural analgesia administrations in a 20-min period. Secondary outcomes included ropivacaine consumption, time of the first patient-controlled epidural analgesia request, duration of the second stage of labor, and incidence of motor block.

Results: Among 210 women randomly allocated the incidence of breakthrough pain was 34.9%, 19.7%, and 13.1%, for groups 4, 6 and 8, respectively ($P = 0.011$). The incidence of breakthrough pain in group 8 was lower than in group 4 ($P = 0.006$). The median (interquartile range) hourly ropivacaine consumption was 8.2 mg/h (7.1–11.3), 10.4 mg/h (9.2–13.0), and 12.0 mg/h (11.2–13.8) in groups 4, 6 and 8, respectively ($P < 0.001$). Group 8 had a longer duration of effective analgesia and longer second stage of labor than group 4. There was no significant difference between groups in the incidence of motor block.

Conclusion: The larger PIEB volumes were preferred for epidural labor analgesia compared with a smaller volume because of improved analgesia without clinically significant increases in adverse effects.

Introduction

Maintenance of epidural labor analgesia using programmed intermittent epidural bolus (PIEB) may be superior to continuous epidural infusion (CEI) analgesia in respects such as reducing the use of local anesthetic, improving the quality of analgesia, reducing motor block, and improving maternal satisfaction.[1–4] In previous studies the incidence of breakthrough pain, defined as the woman complaining of pain or stress requiring supplemental treatment, was as high as 62.3%.[5] Breakthrough pain may adversely affect the maternal labor experience. Many institutions use the PIEB technique for labor analgesia, but the optimal dosage regimen remains unknown.[6–7] Few studies have investigated the analgesic effect of different bolus volumes using the PIEB technique.[7–8] Therefore, we designed a study to evaluate how different bolus volumes affect the occurrence of breakthrough pain in labor analgesia. Our hypothesis was that larger programmed intermittent bolus volumes would reduce the incidence of breakthrough pain compared with smaller volumes.

Methods

This study was a prospective, double-blind, randomized trial approved by the Ethics committee of The Affiliated Hospital of Xuzhou Medical University (XYFY2020-KL218-02). Before starting the intervention, the study was registered at the Chinese Clinical Trial Registry (registration number: ChiCTR2000040450, https://www.chictr.org.cn/showproj.aspx?proj=57445). A convenience sample of patients was recruited from the Affiliated Hospital of Xuzhou Medical Univer-

* Correspondence to: Z. Wang, Department of Anesthesiology, The Affiliated Hospital of Xuzhou Medical University, 99 Huaihai West Road, Xuzhou, Jiangsu, China.
E-mail address: zhpsqxt@163.com (Z.P. Wang).

https://doi.org/10.1016/j.ijoa.2022.103571
Accepted 19 June 2022

sity between 8:00 am and 10:00 pm, and signed informed consent for study participation was obtained.

Women recruited had the following inclusion criteria: (1) nulliparous with term cephalic singleton pregnancies; (2) age ≥18 years; (3) body mass index (BMI) ≤35 kg/m^2; (4) gestational age between 37 and 42 weeks; (5) baseline pain score at time of request for labor analgesia >5 using numerical rating score (NRS 0–10, where 0 indicates no pain, 10 means severe pain); (6) American Society of Anesthesiologists (ASA) physical status II–III.

Exclusion criteria included contraindication to neuraxial block, administration of analgesics and sedatives within two weeks of labor, accidental dural puncture, allergy to study drugs, and patient refusal.

After the eligible parturients entered the labor room, standard monitoring (pulse oximetry, non-invasive blood pressure and fetal tocodynamometry) was initiated and intravenous access was established. The parturient was placed in the left lateral position. The epidural procedure was performed at the estimated L2–3 interspace with a 16-gauge epidural needle using loss of resistance to air, and a 19-gauge multi-orifice epidural catheter was inserted approximately 4 cm into the epidural space. A test dose of 3 mL 1% lidocaine was injected to rule out subarachnoid injection. Epidural analgesia was initiated with 0.1% ropivacaine with sufentanil 0.3 μg/mL 10 mL and analgesia was maintained with the same solution. The sensory block level was measured using an alcohol cotton swab. After 15 min, a woman whose sensory blockade level was below T10 was given an additional 5 mL of the analgesic solution. If, at 30 min, analgesia was inadequate (defined as a pain score >3), the epidural catheter was considered to have failed, and the parturient was excluded from the study.

After the injection of an initial volume of 10 mL of the study solution, the parturient was randomly assigned to one of three analgesia regimens: 4, 6 or 8 mL programmed intermittent epidural boluses every 45 min. Group allocations were generated using a computer-generated random number sequence with a random block size of six and sealed in sequentially numbered opaque envelopes. After the induction epidural dose, the research assistants who were not involved in the data collection set the parameters of the epidural infusion pump and covered the pump with an opaque bag. The participants and anesthetists were blinded to the group allocation.

The infusion pump (Apon ZZB-Ⅳ; Jiangsu Apon Medical Technology, Jiangsu, China, Supplemental Fig. S1) is capable of delivering both PIEB and the patient-controlled epidural analgesia (PCEA) boluses. The bolus infusion rate of the standard tubing is 360 mL/h. The PCEA settings were a bolus of 5 mL with a lockout interval of 10 min in all groups. The infusion limit was 40 mL/h. A 10-min refractory period was programmed between both automated and patient-activated boluses. The parturients were instructed to press the PCEA device button if contractions were uncomfortable. Those who delivered within 60 min of epidural catheter placement were excluded from the final analysis.

Vital signs (heart rate, blood pressure, body temperature, oxygen saturation), motor blockade, pain scores, and sensory block level were recorded every 5 min for the first 30 min, at one hour and two hours, and then every two hours until delivery. Motor block was defined as a modified Bromage score ≤4, wherein score 1 was complete block; score 2 an almost entire block, only able to move feet; score 3 a partial block, just able to move knees; score 4 the detectable weakness of hip flexion, only able to raise leg but cannot keep it raised; score 5 no observable weakness of hip flexion; and score 6 no weakness.[9]

The primary outcome was the incidence of breakthrough pain, defined as parturient perception of inadequate analgesia (defined as a NRS pain score >3) after pushing the PCEA button twice in a 20-min period, and a request for additional analgesia.[1] If breakthrough pain occurred, manual epidural boluses of 1% lidocaine (5–10 mL) were administered. If analgesia was inadequate after at least two manual epidural boluses within 20 min, the epidural catheter was considered to be problematic (such as possible dislodgement), and the case data were removed from the final analysis.

The secondary outcomes were the pain scores, motor blockade, hourly consumption of ropivacaine, time to the first PCEA use, and the duration of the second stage of labor. The hourly consumption of ropivacaine was calculated by dividing the total ropivacaine consumption by the total labor analgesia time (mg/h). The duration of labor analgesia was calculated as the time from pump start to delivery (or at the second stage of labor) or transfer to the operating room for cesarean section. The cervix of the parturient was examined when the parturient requested analgesia. Thereafter, the cervix was checked every two hours or as indicated, according to hospital practice. The duration of the second stage of labor was defined as full cervical dilatation until infant delivery.

Exploratory outcomes included: PCEA use (patients requiring PCEA, PCEA doses); oxytocin augmentation during labor; duration of labor analgesia; adverse effects, including postpartum headache, pruritus, nausea and vomiting; incidence of hypotension (defined as systolic blood pressure < 90 mmHg or >20% decline from baseline); maternal intrapartum fever (defined as body temperature >37.5°C);[10] incidence of membrane rupture; pain with pushing (NRS score); neonatal outcomes; obstetric outcomes; and maternal satisfaction, rated on a 10-point numeric rating scale (0–completely unsatisfied, 10–extremely satisfied). Maternal satisfaction and adverse events were recorded by the same investigator 24 h after epidural catheter placement.

Sample size calculation was performed with PASS 15.0 (NCSS, LLC, Kaysville, USA). The sample size calculation was based on a preliminary trial from 23 patients in our institution. The incidence of breakthrough pain in groups 4, 6, and 8 was 40%, 33%, and 14% respectively. A sample size of 171 achieved 80% power to detect an effect size of 0.24 using a two degrees of freedom chi-squared test with a two-sided significance level (alpha) of 0.05. To account for dropouts, 210 patients were recruited.

Per protocol analysis was undertaken. All data were expressed as mean and standard deviation (SD) or the median (interquartile range) unless otherwise specified. The Kolmogorov-Smirnov test was performed to determine whether continuous data were normally distributed. Variables are described and analyzed according to normal or skewed distributions. Continuous variables were evaluated using analysis of variance (ANOVA) or the Kruskal-Wallis H test. The count data were expressed by proportions, and the chi-squared test or Fisher exact probability was used. The generalized estimation equation (GEE) was established to compare the pain scores of each group at each time point (at 30 min, 60 min, 120 min, 240 min, 300 min, 360 min, 480 min), as well as the average NRS pain scores over time, with baseline NRS scores set as a covariate and Bonferroni correction was used for multiple comparisons. The endpoint of the initial epidural loading dose was recorded as time zero. Time to the first use of PCEA administration is presented as a Kaplan-Meier curve, and differences between the groups were assessed using the log-rank test. Patients who did not push the PCEA button before vaginal delivery or cesarean section were considered to be censored. We defined the time of adequate analgesia as the time from the epidural catheter placement until the first use of PCEA or delivery of the fetus, whichever occurred first. Statistical significance was a two-sided P-value <0.05 except for pairwise group comparisons for which P <0.017 was considered statistically significant where the Bonferroni correction was used. Statistical analysis was performed using SPSS 26.0 (Chicago, IL, USA).

Results

Patients were enrolled from January 2021 to July 2021, with 210 patients randomized and, subsequently, 24 patients excluded from the analysis (Fig. 1). There were no clinically significant differences between groups in baseline characteristics (Table 1).

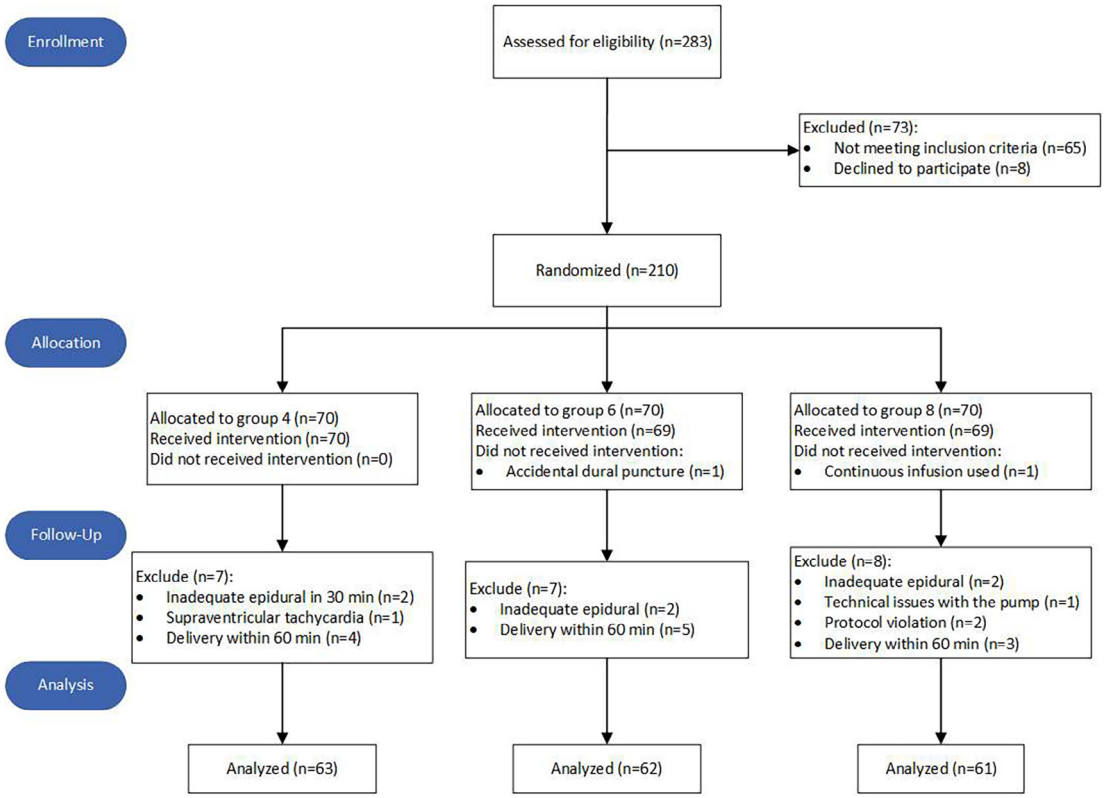

Fig. 1. Flow diagram of the study

Table 1
Baseline characteristics

	Group 4 (n = 63)	Group 6 (n = 62)	Group 8 (n = 61)	*P*-value
Maternal age (y)	27.7 ± 3.1	27.8 ± 3.3	27.4 ± 3.2	0.760
Height (cm)	162.7 ± 5.3	164.0 ± 4.7	162.6 ± 4.8	0.214
Weight (kg)	72.8 ± 8.4	73.7 ± 9.2	73.6 ± 10.7	0.828
Body mass index (kg/m^2)	27.5 ± 3.1	27.3 ± 2.8	27.9 ± 4.1	0.678
Gestational age (d)	276 ± 6	278 ± 6	278 ± 6	0.186
Cervical dilation (cm)	2 (2–2)	2 (2–2)	2 (1.5–2)	0.677
Gravidity	1 (1–1)	1 (1–2)	1 (1–1)	0.126
Baseline NRS (score)	7 (8–9)	8 (7–9)	9 (7–9)	0.156

Values are expressed as mean ± SD or median (interquartile range). NRS: numerical rating scale.

The primary outcome of the study, the occurrence of breakthrough pain, differed significantly among the three groups (Table 2). Pairwise comparisons showed that the incidence of breakthrough pain was significantly lower in group 8 than in group 4 ($P = 0.006$). The number of patients requiring PCEA and the number of requests for PCEA analgesia were also different among the three groups, but there were no statistically significant differences between the pairwise comparisons.

The hourly ropivacaine consumption was significantly different among the three groups (Table 2); the difference in the means between group 8 and group 4 was 3.7 mg/h (95% CI 2.7 to 4.5 mg) ($P < 0.001$); between the group 8 and group 6 was 1.8 mg/h (95% CI 0.9 to 2.6 mg) ($P < 0.001$); between the group 4 and group 6 was 1.9 mg/h (95% CI 1.0 to 2.7 mg, $P < 0.001$).

The comparison of mean pain scores using the GEE showed that the NRS scores were significantly influenced by time ($P < 0.001$) and group ($P = 0.017$) and by the interaction between them ($P < 0.001$). After decomposing the interaction into nested effects, significant differences were identified at specific time points (GEE: 30 min $P = 0.046$; 120 min $P = 0.006$; 240 min $P = 0.002$, Fig. 2). Post-hoc pairwise comparisons showed that the mean NRS score in group 4 was significantly higher than in group 8 at 120 min after epidural injection ($P = 0.005$), and the mean NRS in group 4 was significantly higher than that in group 6 ($P = 0.018$) and group 8 ($P = 0.002$) at 240 min (Bonferroni adjustment for multiple tests).

Kaplan-Meier analysis showed that the difference in the duration until the first use of PCEA among groups was significant (Supplementary Fig. S2, $P = 0.014$ by log-rank test). The pairwise comparisons only showed that group 8 had a longer effective time than group 4 (mean 511 min, 95% CI 221 to 800 min vs. 184 min, 95% CI 102 to 266 min, $P = 0.003$, hazard ratio 2.07, 95% CI 1.26 to 3.39).

A significant difference was observed among the three groups in the duration of the second stage of labor (Table 3). The pairwise comparison results showed that the group 8 duration was significantly longer than in group 4 ($P = 0.004$). Exploratory outcome analyses showed the incidence of episiotomy was significantly different among the three groups (Table 3), and the need for episiotomy was lower in group 4 than that of group 8 after pairwise comparison ($P = 0.007$).

Discussion

The goal of labor analgesia is to achieve satisfactory analgesia without affecting the safety of the mother and fetus, the process of labor,

Table 2
Analgesia characteristics and side effects

	Group 4 (n = 63)	Group 6 (n = 62)	Group 8 (n = 61)	*P*-value
Breakthrough pain	22 (34.9%)	12 (19.4%)	8 (13.1%)	0.011
Patients requiring PCEA	38 (60.3%)	38 (61.3%)	25 (41%)	0.039
PCEA doses				
Total demand[a]	(0, 55)	(0, 42)	(0, 12)	0.033
Successful demand[a]	(0, 14)	(0, 12)	(0, 9)	0.056
Successful-to-total-demand ratio (%)[a,b]	(11, 100)	(8, 100)	(0, 100)	0.686
Oxytocin augmentation	16 (25.4%)	14 (22.6%)	15 (24.6%)	0.931
Bromage score ≤4	0	1 (1.6%)	3 (4.9%)	0.081
Duration of labor analgesia (min)	338 (180–560)	375 (248–608)	343 (205–583)	0.547
Ropivacaine consumption (mg/h)	8.2 (7.1–11.3)	10.4 (9.2–13.0)	12.0 (11.2–13.8)	<0.001
Adverse effects				
Postpartum headache	0	0	0	
Pruritus	10 (15.9%)	12 (19.4%)	12 (19.7%)	0.831
Nausea and vomiting	3 (4.8%)	5 (8.1%)	3 (4.9%)	0.738
Hypotension	0	0	0	
Maternal intrapartum fever	11(17.5%)	11(17.7%)	14 (23.0%)	0.686
Artificial membrane rupture	9 (14.3%)	11 (17.7%)	9 (14.8%)	0.847
Pain with pushing (NRS score)	6 (3–8)	5 (2–7)	5 (2–8)	0.514
Epidural infusion discontinued during the second stage of labor	35 (55.6%)	36 (58.1%)	37 (60.7%)	0.847

Values are expressed as n (%) or median (interquartile range) unless otherwise noted.
[a]Values are expressed as full range. [b]Parturient with PCEA requests: group 4 (n = 38), group 6 (n = 38), group 8 (n = 25).
PCEA: patient-controlled epidural analgesia. NRS: numerical rating scale.

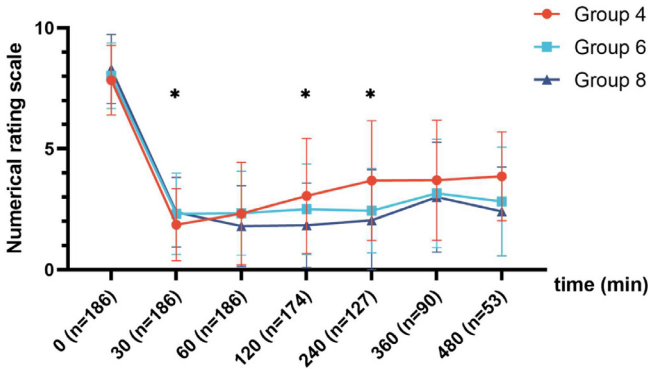

Fig. 2. Numerical rating scale mean pain scores during labor. Error bars are SD. *Significant differences among the three groups. NRS: numerical pain scale

and the outcome of delivery. In this study, we observed the high-volume PIEB regimen resulted in higher anesthetic consumption and longer second stage, but a decreased incidence of breakthrough pain, longer duration of effective analgesia and lower pain scores when compared with the low-volume PIEB regimen.

Sng et al.[11] found that the risk factors for labor breakthrough pain include dysfunctional labor, increased maternal body mass index, and decreased PCEA bolus successful to total demand ratio. The incidence of breakthrough pain was higher than that of Roofthooft et al.'s study,[5] which may be explained by the use of the low epidural bolus volumes, low hourly ropivacaine consumption, and the use of epidural analgesia rather than combined spinal-epidural analgesia.[12] Fidkowski et al.[8] found that the incidence of breakthrough pain was significantly reduced when the interval and injection volumes were larger while maintaining the same hourly dose of local anesthetic. Wong et al.[7] reached a similar conclusion; an increase in bolus volumes and a longer bolus interval reduced the consumption of local anesthetics, possibly due to a reduction in the number of PCEA requests and need for manual rescue analgesia. The PIEB time interval and injection volume seem to be more important in determining analgesia than the total dose per hour of local anesthetic.[7–8] It is suggested that higher injection volumes generate more pressure and promote a more uniform diffusion of the anesthetic solution within the epidural space.

Of note, a recent sequential allocation study by Zhou et al.[13] showed that 90% of parturients did not require additional PCEA bolus or manual bolus when the bolus interval was approximately 42 min for PIEB with a fixed 10 mL dose of 0.08% ropivacaine and sufentanil 0.3 μg/mL. The results of that study were inconsistent with ours, with similar doses in group 8, but 59% not needing a PCEA or physician-

Table 3
Obstetric and neonatal outcomes

	Group 4 (n = 63)	Group 6 (n = 62)	Group 8 (n = 61)	*P*-value
Delivery mode				
Spontaneous vaginal	52 (82.5%)	49 (79.0%)	42 (68.9%)	0.173
Operative vaginal	0	1 (1.6%)	2 (3.3%)	0.215
Cesarean	11 (17.5%)	12 (19.4%)	17 (27.9%)	0.326
Episiotomy[a]	10 (19.2%)	17 (34.7%)	20 (47.6%)	0.025
Duration of second stage (min)	30 (18–43)	38 (28–57)	43 (27–75)	0.006
Apgar score at 1 min	9 (9–9)	9 (9–9)	9 (9–9)	0.428
Apgar score at 5 min	10 (9–10)	10 (9–10)	10 (9–10)	0.998
Neonatal weight (g)	3338 ± 360	3386 ± 357	3376 ± 404	0.674
Satisfaction score for analgesia[b]	9 (9–9)	9 (9–10)	9 (9–10)	0.074

Values are expressed as n (%), mean ± SD or median (interquartile range).
[a] Parturient with non-instrumental delivery, group 4 (n = 52), group 6 (n = 49), group 8 (n = 42).
[b] 11-point scale; 0–completely unsatisfied, 10–extremely satisfied.

delivered top-up. One possible reason for the discrepancy is that the observation period in the Zhou et al.[13] study was limited to six hours, while we observed all stages of labor; 49.5% of women had labor analgesia for more than six hours in our study. In the study by Zhou et al., the median cervical dilation at the end of the study was 7 cm. A positive correlation between pain intensity and cervical dilatation during the first stage of labor has been identfied.[14] Many up-and-down sequential allocation studies only observed the first six hours after initiation of analgesia in the first stage of labor, so the recommended dose may be inadequate for longer labor.[13,15,16] Gradually increasing the bolus volumes of PIEB infusion according to the degree of cervical dilatation may provide more effective analgesia.[17]

We observed that the second stage of labor was longer in group 8 than that in group 4. The difference in means was small, so this time difference is not likely clinically significant. Importantly, analgesia was not provided for many women during the second stage in our study, so these results may not apply when analgesia is continued during the second stage. In the Fidkowski et al. study, although there were no significant differences in Bromage scores among groups, obstetricians thought that some patients in the high PIEB volume groups had a motor block and that this was reflected by the lack of effective second stage pushing.[8] This finding suggests that the Bromage score may not be an ideal method for evaluating motor blocks.[18] Even with low concentrations of local anesthetic, the cumulative effect of doses may lead to prolonged second stage of labor. In addition, the concentrations of anesthetic in our study may cause the women to not feel the urge to push, which may be responsible for the prolonged second stage of labor. Second stage pushing requires supervision by an experienced midwife. We did not control for individual midwives in our trial, which could have affected the results.[19] No additional impact on maternal and neonatal outcomes was observed.

Our exploratory analysis demonstrated that the episiotomy rates were higher in group 8 than in group 4. However, previous studies have shown that the relationship between epidural analgesia and episiotomy is unclear.[20–23] Clesse et al.[22] found that epidural analgesia was one of the risk factors for episiotomy among non-operative vaginal deliveries. At the second stage of labor, Chinese midwives decide whether to perform an episiotomy based on the elasticity of perineal tissue, fetal size, and the urgency of delivery.[24] We therefore speculated that a prolonged second stage of labor may also be associated with these conditions[23,25] which are associated with an increased the incidence of episiotomy. Further, the rate of episiotomy may be related to the skills of midwives. Moderate perineal protection can reduce the incidence of episiotomy.[26] The average episiotomy rate in our institution (30%) was similar to that of a similar population.[27] However, it is still much higher than in North America, where the episiotomy rate has fallen from 17.3% in 2006 to 9.4% in 2011. The American College of Obstetricians and Gynecologists discourage the routine use of episiotomy.[28–29] Finally, there was no significant difference in the incidence of operative vaginal delivery and cesarean section among the three groups. Further comparisons will require more clinical trials to control for confounding factors.

It can be seen from the data that the percentage of patients requiring PCEA decreased with the increase of the bolus volume, but there were no pairwise statistical differences, possibly due to the study being underpowered to identify differences in secondary outcomes. The differences in PCEA requests may also not be clinically significant. Pain scores were higher in group 4 than in group 8 at 120 min, possibly because the effect of the initial epidural dose had begun to diminish. In our study groups, maternal satisfaction was uniformly high, but this can be influenced by many factors during labor.

The current study has some limitations. Firstly, midwives usually stop using the epidural pump at the second stage of labor in our hospital, especially if women do not feel the urge to push. The timing of discontinuation of PIEB analgesia (shortly before or after the programmed bolus) may affect analgesia throughout much of the second stage of labor. We did not record the local anesthetic consumption in the second stage of labor, which is another limitation. Secondly, all participants in this study were nulliparous women, and the results may not be valid for multiparous women. The study was conducted in a single center, and labor analgesia management may differ from other settings. Women with morbid obesity were excluded so it is not known if these results apply to them. Thirdly, we placed the epidural catheter at the estimated L2–L3 interspace. An L2-3 epidural catheter may initially provide more relief of abdominal pain but less relief of perineal labor pain.[30] Finally, the experience of childbirth pain is multidimensional and complex,[31] and assessment of pain with NRS scores ignores the multifaceted nature of women's pain and its location. In this regard, the Angle Labor Pain Questionnaire (A-LPQ) may be a better tool for assessing pain and managing optimal labor analgesia.[32]

In conclusion, our study showed that high bolus volume PIEB with a low concentration of ropivacaine is superior to low bolus volume PIEB for maintaining epidural labor analgesia. However, high doses of local anesthetics may prolong the second stage of labor. The effects of the PIEB interval time and drug concentration on the quality of labor analgesia require further study.

Acknowledgements

We would like to thank the financial support from the Xuzhou Science and Technology Bureau [grant number: KC20053].

Declaration of interests

The authors declare that they have no competing interests.

Funding

This work was supported the Xuzhou Science and Technology Bureau [grant number: KC20053].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijoa.2022.103571.

References

1. Wong CA, Ratliff JT, Sullivan JT, Scavone BM, Toledo P, McCarthy RJ. A randomized comparison of programmed intermittent epidural bolus with continuous epidural infusion for labor analgesia. *Anesth Analg.* 2006;102:904–909. https://doi.org/10.1213/01.ane.0000197778.57615.1a.
2. Ojo OA, Mehdiratta JE, Gamez BH, Hunting J, Habib AS. Comparison of programmed intermittent epidural boluses with continuous epidural infusion for the maintenance of labor analgesia: A randomized, controlled, double-blind study. *Anesth Analg.* 2020;130:426–435. https://doi.org/10.1213/ANE.0000000000004104.
3. Bullingham A, Liang S, Edmonds E, Mathur S, Sharma S. Continuous epidural infusion vs programmed intermittent epidural bolus for labour analgesia: a prospective, controlled, before-and-after cohort study of labour outcomes. *Br J Anaesth.* 2018;121:432–437. https://doi.org/10.1016/j.bja.2018.03.038.
4. Salim R, Nachum Z, Moscovici R, Lavee M, Shalev E. Continuous compared with intermittent epidural infusion on progress of labor and patient satisfaction. *Obstet Gynecol.* 2005;106:301–306. https://doi.org/10.1097/01.AOG.0000171109.53832.8d.
5. Roofthooft E, Barbé A, Schildermans J, et al. Programmed intermittent epidural bolus vs. patient-controlled epidural analgesia for maintenance of labour analgesia: a two-centre, double-blind, randomised study. *Anaesthesia.* 2020;75:1635–1642. https://doi.org/10.1111/anae.15149.
6. Carvalho B, George RB, Cobb B, McKenzie C, Riley ET. Implementation of programmed intermittent epidural bolus for the maintenance of labor analgesia. *Anesth Analg.* 2016;123:965–971. https://doi.org/10.1213/ANE.0000000000001407.
7. Wong CA, McCarthy RJ, Hewlett B. The effect of manipulation of the programmed intermittent bolus time interval and injection volume on total drug use for labor epidural analgesia: a randomized controlled trial. *Anesth Analg.* 2011;112:904–911. https://doi.org/10.1213/ANE.0b013e31820e7c2f.

8. Fidkowski CW, Shah S, Alsaden M-R. Programmed intermittent epidural bolus as compared to continuous epidural infusion for the maintenance of labor analgesia: a prospective randomized single-blinded controlled trial. *Korean J Anesthesiol*. 2019;72:472–478. https://doi.org/10.4097/kja.19156.
9. Nageotte MP, Larson D, Rumney PJ, Sidhu M, Hollenbach K. Epidural analgesia compared with combined spinal-epidural analgesia during labor in nulliparous women. *N Engl J Med*. 1997;337:1715–1719. https://doi.org/10.1056/nejm199712113372402.
10. Chen X, Ni X, Zhang Y, Liu H, Liu Z. The association of labor epidural analgesia with low concentration of ropivacaine and maternal fever: A retrospective study. *J Clin Anesth*. 2020;65:109613. https://doi.org/10.1016/j.jclinane.2019.09.007.
11. Sng BL, Zhang Q, Leong WL, Ocampo C, Assam PN, Sia ATH. Incidence and characteristics of breakthrough pain in parturients using computer-integrated patient-controlled epidural analgesia. *J Clin Anesth*. 2015;27:277–284. https://doi.org/10.1016/j.jclinane.2015.01.003.
12. Nanji JA, Carvalho B. Pain management during labor and vaginal birth. *Best Pract Res Clin Obstet Gynaecol*. 2020;67:100–112. https://doi.org/10.1016/j.bpobgyn.2020.03.002.
13. Zhou S-Q, Wang J, Du W-J, Song Y-J, Xu Z-D, Liu Z-Q. 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. https://doi.org/10.1097/CM9.0000000000000669.
14. Conell-Price J, Evans JB, Hong D, Shafer S, Flood P. The development and validation of a dynamic model to account for the progress of labor in the assessment of pain. *Anesth Analg*. 2008;106:1509–1515. https://doi.org/10.1213/ane.0b013e31816d14f3.
15. Epsztein Kanczuk M, Barrett NM, Arzola C, Downey K, Ye XY, Carvalho JCA. 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. https://doi.org/10.1213/ANE.0000000000001655.
16. Zakus P, Arzola C, Bittencourt R, Downey K, Ye XY, Carvalho JC. Determination of the optimal programmed intermittent epidural bolus volume of bupivacaine 0.0625% with fentanyl 2 g.ml(-1) at a fixed interval of forty minutes: a biased coin up-and-down sequential allocation trial. *Anaesthesia*. 2018;73:459–465. https://doi.org/10.1111/anae.14159.
17. Dai H, Han X, Lv Y, Wu Y, Xu Q, Chen X. Effect of programmed intermittent epidural bolus with stepwise doses of ropivacaine mixed with sufentanil for labor analgesia on the parturients and infants (in Chinese). *J Clin Anesth*. 2020;36:975–979 https://doi.org/10.12089/jca.2020.10.009.
18. Graham AC, McClure JH. Quantitative assessment of motor block in labouring women receiving epidural analgesia. *Anaesthesia*. 2001;56:470–476. https://doi.org/10.1046/j.1365-2044.2001.01524-6.x.
19. Lemos A, Amorim MM, Dornelas de Andrade A, de Souza AI, Cabral Filho JE, Correia JB. Pushing/bearing down methods for the second stage of labour. *Cochrane Database Syst Rev*. 2017;3:Cd009124. https://doi.org/10.1002/14651858.CD009124.pub3.
20. Zhou D, Gong H, He S, Gao W, Wang Q. Effects of combined spinal epidural labor analgesia on episiotomy: a retrospective cohort study. *BMC Anesthesiol*. 2017;17:88. https://doi.org/10.1186/s12871-017-0381-8.
21. Hu LQ, Zhang J, Wong CA, et al. Impact of the introduction of neuraxial labor analgesia on mode of delivery at an urban maternity hospital in China. *Int J Gynaecol Obstet*. 2015;129:17–21. https://doi.org/10.1016/j.ijgo.2014.10.030.
22. Clesse C, Cottenet J, Lighezzolo-Alnot J, et al. Episiotomy practices in France: epidemiology and risk factors in non-operative vaginal deliveries. *Sci Rep*. 2020;10:20208. https://doi.org/10.1038/s41598-020-70881-7.
23. Zeng H, Guo F, Lin B, et al. The effects of epidural analgesia using low-concentration local anesthetic during the entire labor on maternal and neonatal outcomes: a prospective group study. *Arch Gynecol Obstet*. 2020;301:1153–1158. https://doi.org/10.1007/s00404-020-05511-8.
24. Association, MBoMaCHCoC. Guideline of repairing techniques and material selection in episiotomy and perineal tears (in Chinese). *Chin Nurs Manage*. 2019;19:453–457. https://doi.org/10.3969/j.issn.1672-1756.2019.03.027.
25. Laughon SK, Berghella V, Reddy UM, Sundaram R, Lu Z, Hoffman MK. Neonatal and maternal outcomes with prolonged second stage of labor. *Obstet Gynecol*. 2014;124:57–67. https://doi.org/10.1097/aog.0000000000000278.
26. Ma DM, Hu W, Wang YH, Luo Q. A multicentre study on the effect of moderate perineal protection technique: a new technique for perineal management in labour. *J Obstet Gynaecol*. 2020;40:25–29. https://doi.org/10.1080/01443615.2019.1587605.
27. Shen X, Li Y, Xu S, et al. Epidural analgesia during the seconds of labor: A randomized controlled trial. *Obstet Gynecol*. 2017;130:1097–1103. https://doi.org/10.1097/aog.0000000000002306.
28. Ye J, Chen Y, Yang H, et al. A nationwide cross-sectional survey of episiotomy practice in China. *Lancet Reg Heal West Pacific*. 2022;19:100345. https://doi.org/10.1016/j.lanwpc.2021.100345.
29. Kozhimannil KB, Karaca-Mandic P, Blauer-Peterson CJ, Shah NT, Snowden JM. Uptake and utilization of practice guidelines in hospitals in the United States: the case of routine episiotomy. *Jt Comm J Qual Patient Saf*. 2017;43:41–48. https://doi.org/10.1016/j.jcjq.2016.10.002.
30. Moore A, Villeneuve V, Bravim B, et al. The Labor analgesia requirements in nulliparous women randomized to epidural catheter placement in a high or low intervertebral space. *Anesth Analg*. 2017;125:1969–1974. https://doi.org/10.1213/ANE.0000000000002076.
31. Carvalho B, Mhyre JM. Moving beyond the 0–10 scale for labor pain measurement. *Anesth Analg*. 2016;123:1351–1353. https://doi.org/10.1213/ane.0000000000001641.
32. Angle PJ, Kurtz Landy C, Djordjevic J, et al. Performance of the Angle labor pain questionnaire during initiation of epidural analgesia in early active labor. *Anesth Analg*. 2016;123:1546–1553. https://doi.org/10.1213/ane.0000000000001679.