Journal of Anesthesia (2023) 37:945–960
https://doi.org/10.1007/s00540-023-03253-w

REVIEW ARTICLE

Programmed intermittent epidural bolus in maintenance of epidural labor analgesia: a literature review

Fanshu Ni[1] · Ziyi Wu[1] · Ping Zhao[1]

Received: 6 July 2022 / Accepted: 29 August 2023 / Published online: 21 September 2023

Abstract

Programmed intermittent epidural bolus (PIEB), administered by the infusion pump programmed to deliver boluses of epidural solution at certain intervals, is gradually gaining more attention as a technique to maintain the labor analgesia in recent years. Many studies find that it may have some advantages when compared with other methods. However, its exact effectiveness and optimal regimen are still unclear. We conducted a literature search in PubMed, Web of Science, and Cochrane Database of Systematic Reviews for studies published between January 2010 and June 2022. Of the 263 publications identified, 27 studies were included. The purpose of this review is to discuss the effects of PIEB with continuous epidural infusion (CEI) and patient-controlled epidural analgesia (PCEA) in maintenance of epidural labor analgesia on labor outcomes and elucidate the latest research progress of implementation strategies.

Keywords Epidural analgesia · Labor pain · Programmed intermittent epidural bolus · Labor outcome · Strategies

Introduction

Labor pain is considered to be one of the most severe pain in women's life. Although it is not life threatening to healthy puerpera, the pain stress may increase the incidence of postnatal depression [1] and hemodynamic changes can probably have adverse effects on delivery process and fetus [2]. At present, neuraxial analgesia is widely accepted to be the gold standard to alleviate the labor pain. Labor neuraxial analgesia was initially maintained by manual intermittent boluses. Then, CEI, which is a technique using a catheter to provide continuous infusion to the epidural space with or without PCEA, became popular [3]. It was more stable and could reduce supplemental epidural dosage for breakthrough pain [4]. PIEB as a newly emerging technique has been proved by many studies that it resulted in less motor block and higher maternal satisfaction scores [5–7]. This review will examine the effect of PIEB compared with other techniques on labor outcomes, elaborate the latest research progress of the optimum PIEB time interval, epidural catheter type, flow rate, and concentration of local anesthetic, and discuss some concerns when implementing PIEB.

Method

The study was based on an extended literature search performed in the PubMed, Web of Science, and Cochrane Database of Systematic Reviews. Available articles were included from January 2010 and June 2022. The keywords used for the search were programmed intermittent epidural bolus, PIEB, automated mandatory bolus, AMB, labor analgesia, and labor analgesia as well as various combinations of these words. The publications were selected in accordance with the following inclusion criteria: The object of study were women receiving PIEB in maintenance for labor analgesia. The results of the study should include maternal and neonatal outcomes. The exclusion criteria were non-English studies and studies that did not use automated administration of bolus doses. This study primarily employs a literature review methodology, and as such, specific considerations for potential selection bias are not applicable.

Of the 263 publications identified in the search, 27 met the inclusion criteria for this review, including 15 randomized controlled trials, 2 cohort studies, 4 sequential

✉ Ping Zhao
zhaop@sj-hospital.org

[1] Department of Anesthesiology, Shengjing Hospital of China Medical University, No. 36 Sanhao Street Heping District, Shenyang CN 110004, Liaoning Province, China

allocation trials, 2 in vitro studies, 2 systematic reviews, and 2 meta-analyses.

PIEB and other techniques in maintenance of epidural labor analgesia

Labor neuraxial analgesia is usually maintained by CEI, PIEB, or PCEA. Among the three, CEI with or without PCEA is the most widely used method, PIEB became increasingly popular in recent years, and PCEA is usually accompanied with CEI or PIEB, but still some institutions use PCEA without a background infusion [8]. In this section, we will review some studies (Table 1) to compare PIEB, CEI, and PCEA in terms of the quality of analgesia, incidence of motor block, narcotic consumption, mode of delivery, labor process, and Apgar score, and different neuraxial procedures with PIEB make a difference in the maintenance of epidural labor analgesia on labor outcomes.

PIEB vs CEI

Quality of analgesia

There are many indicators to evaluate the quality of analgesia. Commonly used are verbal analogue scale (VAS), maternal satisfaction, PCEA consumption per hour, number of PCEA bolus, and the incidence of breakthrough pain. Ferrer et al. [9] recruited recorded mean VAS score, maternal satisfaction, and percentage of women with breakthrough pain. The results showed no significant difference among the three indicators, but PIEB group demonstrated a trend of lower mean VAS score at each time after epidural and lower incidence of breakthrough pain. Two other randomized trials got the same results in maternal satisfaction [10, 11]. There are also some different conclusions. Riazanova et al. [12] found that at the active labor phase and the active pushing phase, compared with the CEI group, VAS scores in PIEB group declined significantly, and Fan et al. [13] got the similar results. Besides, they also found that the maternal satisfaction score in PIEB group was lower than the CEI group. A 2018 Cochrane [3] and a systematic review [14] approved that PIEB could reduce the incidence of breakthrough pain and the latter indicated that the rate of PCEA usage in PIEB + PCEA group was significant lower than that in CEI + PCEA group (OR, 0.30; 95% CI, 0.16–0.56). Another meta-analysis of randomized controlled trials [15] also found that the VAS score at 30 min, 2 h, 4 h, and 5 h, the rate of breakthrough pain (OR = 0.47, 95% CI: 0.28–0.80, $I^2 = 47\%$) and numbers of patients who require PCEA bolus (OR = 0.27, 95% CI: 0.14–0.51, $I^2 = 65\%$) were lower in PIEB group, besides the satisfaction score of patient was higher compared with the CEI group (WMD = 0.91, 95% CI: 0.42–1.39, $I^2 = 98\%$). In conclusion, compared with CEI, the effect on the quality of analgesia of PIEB may have some advantages, especially in VAS score, incidence of breakthrough pain and PCEA demand. Although some researches did not find significant difference between the two groups, the systematic reviews have the similar results.

Motor block

The high incidence of motor block, which is closely associated with increased use of instrumental delivery, is an important consideration that is widely concerned by obstetricians and anesthesiologists. Unfortunately, there is no consistent conclusion at present. Ojo et al. [10] involved 120 parturient and found that the Bromage score in the CEI group started to be significantly lower than PIEB in 4 h after the loading dose and the linear mixed-effect model demonstrated that the Bromage scores in CEI group were increasingly lower over time than the PIEB group. A prospective cohort study [16] assessed the prevalence of lower limb motor block (Bromage scale grade II-IV) every two hours and found that the prevalence in PIEB + PCEA group was significantly lower compared with the CEI group. However, Haidl and colleagues [11] found no statistical difference in the modified Bromage score at both 60 min and delivery. Ferrer et al. [9] compared the modified Bromage scale of PIEB with CEI at 15 min post-epidural and at every following hour until delivery. The results also showed no significant difference in motor unilateral block, while the incidence of motor blockade in CEI group at each time point was all higher than PIEB group. The conflicting evidence regarding the motor block might be related to the different end point of the studies. Although Ojo et al. [10] got the significant different results, the significant difference appeared 4 h after the loading dose while studies found no significant difference measured by the Bromage scores up to 3 h or at delivery (no clear time point). We can infer from these studies that there is no significant difference in the incidence of motor block between the two methods within 4 h and after 4 h, the prevalence of motor block using PIEB may be lower than using CEI.

Narcotic consumption

It is widely agreed that PIEB reduces the local narcotic consumption. Fan et al. [13] recruited 3000 parturients and the results indicated that the dosage of both ropivacaine and sufentanil in PIEB group decreased significantly. Several other randomized controlled studies and three systematic reviews found the similar results [3, 9, 12, 14–17]. Although Haidl et al. [11] found no difference in the total hourly consumption of the epidural solution between the two methods, PIEB group also had a tendency toward more bupivacaine rescue boluses. Moreover, the sample size of the study

Table 1 Clinical trials comparing PIEB with CEI or PCEA

Study	Neuraxial analgesia initiation	Epidural solution	CEI/PCEA regimen	PIEB regimen	PIEB infusion rate	Pump	Catheter type	PCEA regimen	Positive result
Capogna et al. [6]	20 mL 0.0625% levobupivacaine with sufentanil 10µg	0.0625% levobupivacaine 0.5µg/mL sufentanil	10 ml/h	10 ml bolus/h + PCEA	–	2 pumps (GemStar; Hospira, Lake Forest, IL)	Closed-end, multi-orifice epidural catheter	5 ml boluses lockout interval 10 min	Less incidence of instrumental delivery, lower total anesthetics consumption, number of patients requiring additional PCEA boluses, and mean number of PCEA boluses per patient in PIEB group
Ferrer et al. [9]	10 mL 0.1% bupivacaine	Bupivacaine 0.1% fentanyl 2 µg/mL	10 mL/h	10 mL bolus /h	125 mL/h	Sapphire™ Epidural infusion pump (Sapphire Pump, Hospira, Lake Forrest, IL, USA)	–	–	Lower anesthetic consumption in PIEB group
Ojo et al. [10]	20 mL 0.1% ropivacaine with 2 µg/mL fentanyl	0.1% ropivacaine 2 µg/mL fentanyl	8 mL/h	6 mL bolus/45min + PCEA	250 mL/h	CADD-Solis ambulatory infusion pump (Smiths Medical, Minneapolis [4], MN)	Multiport catheter	8 mL boluses lockout time 10 min	Higher median PCEA attempts per given ratio per hour and less motor block in PIEB group
Haidl et al. [11]	10 ml 1 mg/ml bupivacaine, 2µg/ml fentanyl 2µg/ml adrenaline	Bupivacaine 1mg/ml, fentanyl 2 mcg/ml, adrenaline 2 mcg/ml	5ml/h + PCEA	5 ml/h bolus + PCEA	100 ml/h	Rythmic pump (Micrel Medical devices S.A. Pallini, Greece)	Multi-orifice catheter	5 ml bolus lockout time 20 min	Lower number of successfully administered PCEA boluses in PIEB group
Riazanova et al. [12]	10 ml 0.08% ropivacaine	0.08% ropivacaine hydrochloride	8ml/h + PCEA	8 ml bolus/30min + PCEA	–	Mini Rythmic Evolution (Micrel Medical Devices SA, Athens, Greece)	–	8.0 ml bolus, lockout interval 30 min	Lower VAS score at active labor phase and the active pushing phase, lower anesthetic consumption, longer time to first bolus requested in PIEB group

Table 1 (continued)

Study	Neuraxial analgesia initiation	Epidural solution	CEI/PCEA regimen	PIEB regimen	PIEB infusion rate	Pump	Catheter type	PCEA regimen	Positive result
Fan et al. [13]	10 ml 0.125% ropivacaine plus 0.4μg/ml sufentanil	0.08% ropivacaine plus 0.4μg/ml sufentanil	10ml/h + PCEA	10 ml bolus/h + PCEA	–	ZZB-I for CEI ZZB-II for PIEB (Jiangsu Aipeng Medical Science and Technology Company Ltd., Nantong, China)	Closed-end, multi-orifice catheter	5 ml boluses lockout interval 30 min	Lower incidence of maternal fever from 4 h post-analgesia to delivery, lower pain scores at 3, 4, 5 h post-analgesia and delivery, lower number and proportion of PCEA demand, and anesthetics consumption, higher epidural sensory levels 2 h post-analgesia and satisfaction score in PIEB group
Lin et al. [17]	10 mL 0.15% ropivacaine	0.1% ropivacaine 0.3μg/mL sufentanil	5 ml/h + PCEA	5 ml bolus/h + PCEA	–	–	–	5 mL bolus lockout interval 20 min	Lower VAS score and epidural anesthetic total consumption in PIEB group
Bullingham et al. [16]	15–20ml 0.125% bupivacaine with fentanyl 5μg/ml	Ropivacaine 0.1% fentanyl 2μg/ml	ropivacaine 0.2% fentanyl 2mg/ml (5–15 ml /h)	5 ml bolus /h + PCEA	250 ml/h	CADD®-Solis epidural pump (Smith Medical, MN, USA)	–	5 ml bolus 10 min lockout period	Fewer patients with motor block, shorter second stage of labor for primiparous women, less anesthetic consumption in PIEB group

Table 1 (continued)

Study	Neuraxial analgesia initiation	Epidural solution	CEI/PCEA regimen	PIEB regimen	PIEB infusion rate	Pump	Catheter type	PCEA regimen	Positive result
Holgado et al. [18]	4 ml twice with a 5-min interval 0.1% ropivacaine plus 2 µg/mL fentanyl	0.1% ropivacaine 2 µg/mL fentanyl	0.2% ropivacaine + 100-µg fentanyl initial bolus 8–10 ml/h	60 min interval + PCEA the volume was adjusted depending on the woman's height	250 ml/h	CADD®-Solis epidural pump (Smiths Medical, Minneapolis, MN, USA)	Multi-perforated epidural catheter	Lockout interval 20 min the volume was adjusted depending on the woman's height	Fewer cesarean sections and instrumental deliveries, lower anesthetics consumption, higher maternal satisfaction in PIEB group
Lim et al. [22]	2ml of fentanyl 25 µg with normal saline	levobupivacaine 0.1% with fentanyl 2 lg/mL	10 ml/h	5 ml bolus/30 min	–	Rythmic™ Pump Micrel Medical Devices S.A. Pallini Greece-European Union	Multi-orifice catheter	–	The bolus group had a lower incidence of breakthrough pain and significantly higher satisfaction scores than the infusion group
Roofthooft et al. [23]	4 ml 4.8 mg of ropivacaine and 3µg of sufentanil	0.12% ropivacaine 0.75µg/ml sufentanil	5 ml boluses with a 12 min lockout interval	10 ml bolus/h + PCEA	250 ml/h	–	Multi-orifice catheter	5 ml boluses lockout interval 20 min	Less frequent breakthrough pain, less incidence of motor block, greater local anesthetic consumption, fewer patient-controlled epidural analgesia boluses in PIEB group
Bourges et al. [24]	10 mL of 0.625 mg/mL of levobupivacaine and 5 µg of sufentanil	levobupivacaine 0.625 mg / mL with 50 µg of sufentanil and 75 µg of clonidine	8 mL boluses with a lockout period of 8 min	8 ml bolus/h + PCEA	8 mL over 3 min	CADD-Solis ambulatory infusion pump, Smiths Medical France, Rungis, France	Multi-orifice catheter	8 ml boluses lockout interval 8 min	The median hourly consumption of levobupivacaine was significantly lower in the PCEA group compared to the PCEA + PIEB group

Table 1 (continued)

Study	Neuraxial analgesia initiation	Epidural solution	CEI/PCEA regimen	PIEB regimen	PIEB infusion rate	Pump	Catheter type	PCEA regimen	Positive result
Song et al. [25]	10 mL of 0.1% ropivacaine with 0.3 μg/mL of sufentanil (dural puncture epidural technique)	0.1% ropivacaine with 0.3 μg/mL of sufentanil	8 mL/h	10 ml bolus/h + PCEA	–	Apon MC ZZB-I; Jiangsu Apon Medical Technology	Multi-orifice catheter	5 ml boluses lockout interval 20 min	DPE + PIEB achieved a greater anesthetic drug-sparing effect and superior analgesia quality than EP/DPE + CEI without increasing maternal or neonatal side effects

reflects the possibility that a larger sample size would have brought about a statistically difference.

The mode of delivery

The results from observational studies are contradictory. A cohort study conducted by Holgado et al. [18] compared CEI versus PIEB + PCEA and assessed the mode of delivery as the primary outcome found that the number of cesarean sections and instrumental deliveries in PIEB + PCEA group was significantly lower after correcting for confounders. In contrast, Bullingham et al. [16] found no significant difference in the mode of delivery. The results of randomized controlled trials are also inconsistent. Three randomized controlled trials did not found statistic difference in instrumental vaginal delivery rates and cesarean delivery rates between PIEB and CEI [9, 13, 17]. A Cochrane review [3] confirmed the results (risk of cesarean delivery: RR 0.92, 95% CI 0.70 to 1.21, $I^2 = 0\%$ and risk of instrumental delivery: RR 0.75, 95% CI 0.54 to 1.06, $I^2 = 0\%$) However, Capogna et al. [6] and another systematic review [14] indicated a statistically lower incidence of instrumental delivery using PIEB (OR, 0.51; 95% CI, 0.30–0.84, $I^2 = 24\%$). As Bullingham et al. [16] put forward in the study that the rates of instrumental delivery observed in their study and previous randomized controlled trials (RCTs) demonstrated a consistent trend toward less incidence of instrumental delivery, we also find the same trend in the most of the above studies. Furthermore, the mode of delivery in all of these studies except Holgado et al. [18] was assessed as the secondary outcome. Therefore, more studies with the delivery mode as the primary outcome, confounders corrected and larger sample size should be conducted in future to determine the effects of PIEB and CEI on delivery mode, especially the incidence of instrumental delivery.

Labor process

Studies that have investigated this parameter have conflicting results. The Cochrane review and four RCTs [3, 6, 9, 10, 12] discussed the whole labor process, Fan et al. [13] studied the first stage of labor, and a RCT [17] considered the first and second stage of labor had no significant difference between PIEB and CEI. In contrast, in the meta-analysis by Xu et al. [14], the length of total and first and second stage of labor were all shorter using PIEB compared with CEI (15, 11, and 3 min), but the differences were hardly clinically significant. Liu et al. [19] and Wang et al. [15] got the similar findings with the former's difference of total and first and second stage of labor 21.46, 13.41, and 4.98 min, respectively, and the difference of the first and second stage of the latter was 10.52 and 1.48 min, respectively. For the subgroup analysis of the meta-analysis [3], the results of subgroup that utilized

PCEA showed that PIEB probably reduced the duration of labor analgesia (MD − 13.24 min, 95% CI − 20.71 to − 5.76, $I^2=0\%$) compared with CEI, while the subgroup that did not utilize PCEA found little or no difference in the duration of labor analgesia between the two methods (MD − 48.65 min, 95% CI − 129.92 to 32.62, $I^2=73\%$). The subgroups analysis of Liu et al. [19] indicated that the significant difference found in first and second stage of labor was mainly detected in parturients who received PCEA, while the results of total duration of labor remained irrespective of PCEA status. Considering that most institutions use PIEB or CEI together with PCEA for labor analgesia, PIEB can reduce the labor process, but there is little clinical significance.

Apgar score

In the four studies that reported Apgar scores [9, 12, 13, 17], one reported Apgar scores at 1, 5, and 10 min and three studies reported Apgar scores at both 1 and 5 min. None of the studies showed any significant difference in Apgar scores between the two techniques. These findings were confirmed in the meta-analysis by Sng et al. [3] and Xu et al. [14]. However, a meta-analysis that involved 15 studies [15] found that the Apgar score at 1 and 5 min in PIEB group was significantly higher than that of CEI group (WMD = 0.07, 95% CI: 0.02 to 0.12, $I^2=49\%$) (WMD = -0.08, 95% CI: −0.12 to −0.05, $I^2=21\%$). In these three meta-analyses, Wang et al. [15] had the highest number of included studies, while the other two studies only reviewed the data qualitatively due to high heterogeneity. The Apgar score has been typically compared as the secondary outcome, and the small sample size may be the reason why previous studies did not find statistically significant differences.

Epidural distribution

Current thinking suggested that better analgesic effect and lower total consumption of local anesthetic using PIEB might be associated with a wider sensory block and better homogeneous distribution compared with CEI. Hogan [20] studied three human bodies by injecting ink through epidural catheters inserted by standard techniques. After freezing and microtome sectioning, they found that rather than as a unified advancing front, the spread of solution is directed among paths between structures according to pressures by which they are compressed. This indicated that when large volumes and correspondingly high injectate pressure near the site of injection engage numerous channels, spread is most uniform. Mowat et al. [21] injected aqueous dye (1 ml) into the epidural catheter as a bolus or as an infusion over 30 min in seven anaesthetized pigs and compared the extent of dye spread. The results showed that bolus injection in a porcine model provided greater spread within the epidural space than delivery by infusion (15.2 ± 2.7 cm vs 8.9 ± 2.6 cm). This could result from the greater injection pressures. Many clinical trials agreed the above conclusions [10, 12, 17, 22].

PIEB vs PCEA

To our knowledge, few articles have been published to compare PIEB with PCEA without a background infusion. A two-center, double-blind, randomized study [23] compared the effect of PIEB and PCEA on labor analgesia. They randomized 130 nulliparous to PIEB group and PCEA group. Both groups used ropivacaine 0.12% with sufentanil 0.75 μg/ml and the same potential maximum volume per hour. The results showed that patients in PIEB group had reduced frequent breakthrough pain, fewer motor block, and greater local narcotic consumption with fewer PCEA boluses. Bourges et al. [24] also compared PCEA and PIEB. The maintenance solution levobupivacaine 0.625 mg/mL, sufentanil 0.25 mg/mL, and clonidine 0.375 mg/mL. They found that PCEA-only resulted in lower hourly consumption of local anesthetic, but the difference was not clinically relevant. Yet it is worth noting that, in both studies, the PIEB group also had on-demand patient-controlled epidural analgesia boluses instead of using PIEB-only. In Roofthooft et al. [23] study, the lockout interval of PCEA regimen in PIEB group was 20 min, longer than PCEA group with a 12 min lockout interval, while Bourges et al. used the same PCEA regimen in the two groups.

Different neuraxial procedures with PIEB

The dural puncture epidural (DPE) technique is a relatively new method for neuraxial labor analgesia. Due to its advantages such as fast onset, better sacral spread and fewer side effects compared to traditional epidural and combined spinal epidural techniques, it has received increasing attention in recent years. At present, there is relatively little research on the combination of DPE and PIEB. Song et al. [25] randomized 116 women to receive EP + CEI, DPE + CEI, and DPE + PIEB for labor analgesia. The result demonstrated that compared with EP/DPE + CEI, the use of DPE + PIEB achieved a greater anesthetic drug-sparing effect and superior analgesia quality without increasing maternal or neonatal side effects. This indicated that DPE + PIEB is a superior option for future labor analgesia. Epidural analgesia (EP) and combined spinal epidural (CSE) analgesia are currently mature and widely used neuraxial procedures. As mentioned earlier in our text, whether EP or CSE is used, the labor outcome of PIEB is better than that of CEI. We did not find studies compared EP, CEI or DPE when using PIEB as maintenance of epidural labor analgesia.

Implementation strategies

The time interval of PIEB

Since one of the biggest differences between PIEB and CEI is that the local anesthetic solution of PIEB is automatically administered at a fixed time interval, time interval is a noticeable parameter in PIEB regimen strategies. The optimal PIEB regimen is still unclear, and the implementation strategies vary among institutions and studies. In the institutions that implement PIEB, the time interval is generally 30–60 min, of which 60 min is the most common. To determine how PIEB interval and volume influence the labor outcome, some institutions conducted relevant researches (Table 2). Wong et al. [26] randomized 190 healthy nulliparous women to 1 of 3 maintenance regimens of PIEB: 10 mL every 60 min (10/60), 5 mL every 30 min (5/30), or 2.5 mL every 15 min (2.5/15). The epidural maintenance solution was bupivacaine 0.625 mg/ml and fentanyl 1.95 μg/ml. The primary outcome, median (interquartile range) adjusted bupivacaine consumption per hour of labor was 8.8 mg in group 10/60 compared with 10.0 mg in group 5/30 and 10.4 mg in group 2.5/15, and no difference was found in the pain scores at delivery, number of manual bolus doses for breakthrough pain, PCEA requests or administrations, time to first PCEA, and patient satisfaction.

Investigators from Mount Sinai Hospital, University of Toronto, performed three biased-coin up-and-down sequential allocation trials [27–29] to obtain the effective interval 90% for the PIEB regimen (EI90) to find the optimal interval time. Their first study [27] involved 40 nulliparous women who underwent spontaneous or induced labor. The 0.0625% bupivacaine plus sufentanil citrate solution 2 μg/ml was used as the maintenance solution. In all subjects, the PIEB dose was fixed at 10 mL. The PIEB interval for the first patient was set at 60 min, and the subsequent patients' PIEB intervals were set at different intervals (60, 50, 40, and 30 min; 60, 50, 40 and 30 groups, respectively). The results demonstrated that the optimal time interval was approximately 40 min, nearly 70% of the patients in group 30 had sensory block above T6, while in groups 40, 50, and 60, the percentage was 44%, 22%, and 11%, respectively. The bupivacaine solution used this study is similar to Wong et al., and the main difference between the two studies is the total volume of bupivacaine solution in each group and whether PCEA or manual bolus was used to prevent breakthrough pain. Since 44% of women in the first study experienced upper sensory block to ice above the T6 level, which suggested that the spread of the epidural mixture was exaggerated and unnecessary, they designed another research to discuss during the first stage of labor, the effective PIEB time interval between 5 mL boluses of bupivacaine 0.125% with fentanyl 2 μg/ml. The second study [28] used the same method and found that the EI90 was approximately 35 min, 20/40 women had an upper sensory block above T6, no motor block appeared in 34/40 women, and no hypotension treatment was required. They then conducted a third study [29] to determine the EI90 for the PIEB boluses of 2.5 mL of 0.25% bupivacaine plus fentanyl 8 μg/ml. The results demonstrated that the estimated EI90 was 20 min, beyond their estimated hypothesis which was 30–60 min. Another result contrary to their assumption was that the consumption of local anesthetic with this regimen was higher than in their previous studies. Zhou et al. [30] also adopted the same method as the above two articles to investigate the optimal duration with 10 ml of ropivacaine 0.08% and sufentanil 0.3 mg/mL which is the standard treatment for labor pain in China. The optimal PIEB interval was about 42 min, and the incidence of maximum sensory block level above T6 was 20%, 5.3%, 0%, and 0% of parturients in groups 30, 40, 50, and 60, respectively. They compared their study with Epsztein et al. [27] which used the same duration of time intervals and bolus volumes and found that the incidence of motor blockade decreased statistically.

Li et al. [31] studied the relationship of body temperature between PIEB at different intervals combined with PCEA. They randomly divided 170 primiparous women into group A (5 ml/30 min) and group B (10 ml/60 min). The maintenance dose was 0.075% ropivacaine and 0.5 μg/ml sufentanil. Maternal temperature in group A was higher than that in group B at the time of cervix being completely dilated and 2 h after delivery. The incidence of intrapartum fever, VAS score, serum TNF-α, IL-6, CRP levels and epidural analgesic dosage at two hours after delivery in group A were all higher than those in group B.

From these studies, the body temperature and incidence of postpartum fever was lower with fewer anesthetics used at intervals of 60 min than at intervals of 30 min or less in PIEB + PCEA mode. The optimal interval of 10 mL of bupivacaine 0.0625% with fentanyl 2 μg/mL, 5 mL boluses of bupivacaine 0.125% with fentanyl 2 μg/ml, 10 ml of ropivacaine 0.08% and 0.3 mg/mL sufentanil, and 2.5 mL of 0.25% bupivacaine plus fentanyl 8 μg/ml in PIEB is 40, 35, 42, and 20 min, respectively. With the above-discussed results, we refer that when the deliver bolus is 10 ml, the optimal intervals are similar, around 40 min, regardless of the kind of the drugs. When the single bolus becomes smaller, the optimal interval gets shorter. Since the commonly used drug concentration is about 0.1% and the commonly used single dose is 5 ml or 10 ml, we recommend that the optimal interval can be between 35–40 min. However, since all of these studies only included nulliparous women and first stage of labor, more studies should be done to

Table 2 Clinical trials on implementation strategies

Study	Study design	Neuraxial analgesia initiation	Epidural solution	PIEB regimen	PIEB infusion rate	Pump	Catheter type	Positive result
Wong et al. [26]	RCT	Bupivacaine 1.25 mg and fentanyl 15 µg	Bupivacaine 0.625 mg/mL with fentanyl 1.95 g/mL	2.5 mL every 15 min (2.5/15), 5 mL every 30 min (5/30), or 10 mL every 60 min (10/60)	300mL/h	Hospira Gemstar infusion pump (Hospira, Inc., Lake Forest, IL)	Single-orifice epidural catheter	The median adjusted bupivacaine consumption per hour of labor was 8.8 mg (8.0–9.7 mg) in group 10/60 compared with 10.0 mg (9.3–10.8 mg) in group 5/30 and 10.4mg (9.6–11.2mg) in group 2.5/15
Kanczuk [27]	Biased-coin up-and down sequential allocation trial	Loading dose of 12 mL of 0.125% bupivacaine with fentanyl 3.3 µg/mL	bupivacaine 0.0625% with fentanyl 2 µg/mL	10 mL boluses with the studied time intervals of 60, 50, 40, and 30 min	–	CADD-Solis ambulatory infusion system (Smith Medical, St Paul, MN)	Multiport wire-reinforced epidural catheter	The EI interval 90% was 42.6 min using the truncated Dixon and Mood method and 36.8 min using the isotonic regression analysis
Bittencourt et al. [28]	Biased-coin up-and down sequential allocation trial	Loading dose of 12 mL bupivacaine 0.125% with fentanyl 3.3µg/ml	Bupivacaine 0.125% with fentanyl 2 lgmL-1	5 mL boluses with the studied time intervals of 60, 50, 40, and 30 min	250mL/h	CADD-Solis ambulatory infusion system (Smith Medical, St. Paul, MN, USA)	Multiport wire-reinforced epidural catheter	The estimated EI90 was 36.5 min,20/40 women had an upper sensory block to ice above T6, 34/40 women had no motor block
Shatalin [29]	Biased-coin up-and down sequential allocation trial	12 mL of 0.125% bupivacaine with fentanyl 3.3µg/ml	0.25% bupivacaine plus fentanyl 8 µg/ml	2.5 mL boluses with the studied time intervals of 60, 50, 40, and 30 min	250ml/h	CADD®-Solis Ambulatory Infusion System (Smith Medical, St Paul, MN, USA)	Closed-end, multi-orifice, wire-reinforced epidural catheter	The estimated EI90 was 20 min the median upper sensory block for women in the 30-min group and more than 30 min were T6 (or T5) and T7, respectively

Table 2 (continued)

Study	Study design	Neuraxial analgesia initiation	Epidural solution	PIEB regimen	PIEB infusion rate	Pump	Catheter type	Positive result
Zhou et al. [30]	Biased-coin up-and-down sequential allocation trial	10 mL of ropivacaine 0.08% with sufentanil 0.3 µg /mL	Ropivacaine 0.08% with sufentanil 0.3 µg /mL	10 mL boluses with the studied time intervals of 60, 50, 40, and 30 min	–	–	–	The estimated optimal interval was 44.1 min and 39.5 min using the truncated Dixon and Mood method and isotonic regression analysis, respectively. The maximum sensory block level above T6 was in nearly 20% of parturients in group 30; however, 5.3%, 0%, and 0% of the parturients presented with sensory block level above T6 in groups 40, 50, and 60, respectively

Table 2 (continued)

Study	Study design	Neuraxial analgesia initiation	Epidural solution	PIEB regimen	PIEB infusion rate	Pump	Catheter type	Positive result
Li et al. [31]	RCT	0.075% ropivacaine and 8 mL of sufentanil citrate solution 0.5 μg /mL	–	5 mL every 30 min and 10 mL every 60 min	–	–	–	Maternal temperature in Group A (30 min interval) was higher than that in Group B (15 min interval) at the time of cervix being completely dilated, and 2 h after delivery. Incidence of intrapartum fever in Group A was higher than that in Group B Epidural analgesic dosage, VAS score, serum CRP, TNF-α, and IL-6 levels in Group A were higher than those in Group B at two hours after delivery
Lange et al. [34]	RCT	fentanyl 25 μg (concentration: 50 μg/ml)	Bupivacaine 0.625mg/ml with fentanyl 1.95 μg/ml	10 ml every 60min	100 ml/h or 300ml/h	CADD-Solis Pain Management System v3.0 with Programmed Intermittent Bolus (PIB) Model 2110 (Smiths Medical)	single-orifice epidural catheter	Provider-administered supplemental bolus doses were requested by 44 of 108 (40.7%) in the low- and 37 of 102 (36.3%) in the high-rate group

Table 2 (continued)

Study	Study design	Neuraxial analgesia initiation	Epidural solution	PIEB regimen	PIEB infusion rate	Pump	Catheter type	Positive result
Mazda et al. [35]	RCT	15 mL of bupivacaine 0.125% with fentanyl 3.3μg/ml	Bupivacaine 0.0625% plus fentanyl 2 μg/ml	10ml every 40min	125ml/h or 250ml/h	CADD-Solis ambulatory infusion system (Smith Medical, St. Paul, MN, USA)	Closed-end multi-orifice, wire-reinforced epidural catheter	The proportion of women presenting sensory block T6 at any time and the median highest sensory block level was not different between the groups. Women in the G125 group had a lower incidence of hypotension. Quality of analgesia and patient satisfaction were not different between groups

clarify whether the results are available for the whole process of labor and all parturients.

Epidural catheter type and bolus infusion rate

The bolus infusion rate and catheter type are the possible factors that affect the analgesic effect in PIEB regimen as well. The common infusion rate is 100-400 ml/h, and the catheter type also varied among institutions. Since the presumed advantages of PIEB compared with CEI result from larger volumes and more uniform distribution of solution in the epidural space [20], two in vitro studies [32, 33] (Table 3) discussed the relationship between delivery speeds, catheter type and bolus injection pressure.

The first one [32] performed 660 measurements to evaluate the pressure and flow characteristics of 11 commonly used epidural catheters according to the PIEB regimen. They measured the pressure at flow rates of 100, 250, and 400 ml/h with a bolus volume of 10 ml. The results demonstrated that the pressure increased 1.31, 1.65, and 2.00 mmHg for 18G, 19G, and 20G catheters, respectively, per 1 ml/h of increased flow rate. Analyses contained wire-reinforced catheters which indicated that the pressure of 18G, 19G and 20G catheters increased by 1.16 mmHg, 1.76 mmHg, and 2.36 mmHg, respectively, for each additional 1 ml/h flow rate. These findings indicate that higher gauged catheters, higher flow rates, and wire-reinforced catheters generate higher pressures. The equipment may also influence the maximum pressure since different infusion pumps have different threshold for occlusion alarms. In addition, the combination of a high flow rate and increased catheter gauge may trigger the occlusion alarm. The study only tested multi-orifice epidural catheters.

The second one [33] used four epidural catheters (2 single hole and 2 multi hole) to test the pressure generated by normal saline delivery at 100, 175, 300, and 400 ml/h. No matter used single-orifice or multi-orifice catheters, the peak pressure increased with the increase in the infusion speed and at all infusion speeds, the peak pressure of multi-hole catheters was higher than that of single-orifice catheters, although the difference was small.

To confirm how the bolus delivery rates influence the quality of analgesia in human, Lange et al. [34] (Table 2) conducted a RCT to find how does the infusion bolus delivery rate affect labor analgesia. They recruited 108 nulliparous women and randomized them to the low-rate (100 ml/h) and the high-rate (300 ml/h) group. The maintenance epidural solution was bupivacaine 0.625 mg/ml with fentanyl 1.95 μg/ml, with the 60 min interval each bolus (10 ml). The results showed no significant difference in the hourly bupivacaine consumption and patient requested/delivered epidural bolus ratio between groups which indicated that epidural bolus delivery rates were not related to labor

Table 3 In vitro studies

Study	Group	Solution	Positive result
Krawczyk et al. [32]	100, 250 and 400 mL/h	10 mL plain 0.1% concentration bupivacaine	The interaction between the flow rate and catheter gauge resulted in 1.31, 1.65, and 2.00mm Hg of pressure increase for 18G, 19G, and 20G catheters, respectively, per 1 mL/h of increased flow rate. Analyses including wire-reinforced catheters revealed a 1.16, 1.76, and 2.36mm Hg pressure increase for 18G, 19G, and 20G catheters, respectively, per 1 mL/h of increased flow rate
Klumpner et al. [33]	100, 175, 300, and 400 mL/h	10 mL of infusate (0.9% normal saline)	Peak pressure increased with increasing delivery speeds in both catheter groups. Peak pressures were higher with the multi-orifice catheter compared with the single-orifice catheter at all delivery speeds

analgesia quality. Another RCT [35] (Table 2) involved 90 nulliparous women and randomized them to receive PIEB delivered at 250 mL/h (G250) or 125 mL/h (G125). Analgesia was sustained using a mixture of 0.0625% bupivacaine and 2 μg/ml fentanyl, with the PCEA boluses administered at 10 mL intervals every 40 min. The results of the study also demonstrated that different infusion rates of PCEA provided comparable analgesic effect. Furthermore, the researchers observed that women in the G125 group had a lower incidence of hypotension (11.1% vs 33.3%; $P=0.01$). It is worth noting that, in both studies, the median bupivacaine consumption decreased approximately 0.9 mg/h although it is not statistically different and it suggests a potential advantage of employing a higher infusion rate; larger sample size may obtain different results. Considering the results of the two studies and higher rates of infusion (greater than 250 ml/h) require a high-flow tubing to achieve optimal flow dynamics with PIEB which may increase the cost, a lower infusion rate may be preferable. However, there is still relatively little research on this topic. The infusion rates compared in the two articles were different, and the patients involved in the above studies were nulliparous women and warrant further investigation.

From these studies, the higher flow rate, higher gauged catheters, and wire-reinforced catheters can generate higher pressure. Multi-orifice catheter can also result in higher pressure compared with single-orifice catheter, and the equipment may influence the maximum pressure. However, the above conclusions are obtained in vitro condition where the pressure, volume and compliance are different from the epidural space but may have an impact on the distribution of solution, and the safe peak pressure in the human epidural space remains unknown. Current clinical studies have not found that the increased infusion rate can improve the quality of labor analgesia. Despite the result of the clinical study and in view of the common speculation, we consider that higher gauged, wire-reinforced and multi-orifice catheters are better. For the flow rate, considering the cost, the bolus delivery rates lower than 250 ml/h may be appropriate. Further studies are required to figure out the relationship between bolus infusion rate, catheter type, pressure generated during PIEB injection, and analgesic effect and set the optimal value.

Concentration of local anesthetic

Previous studies suggested that low concentrations of local anesthetics (≤ 0.1% bupivacaine, 0.1% levobupivacaine, or ≤ 0.17% ropivacaine) had some advantages compared with high concentrations of local anesthetics. A meta-analysis published by Sultan et al. [36] showed that low concentrations were associated with a lower incidence of assisted vaginal delivery (OR = 0.70; 95% CI 0.56 to 0.86; $I^2=0\%$), less motor block (OR 3.9; 95% CI 1.59 to 9.55; $I^2=55\%$) and a shorter second stage of labor (WMD-14.03; 95% CI-27.52 to-0.55; $I^2=93\%$). Another systematic review identified nine RCTs [37] that found no differences in the risks of assisted vaginal delivery (OR = 1.18; 95% CI, 0.93–1.49, $I^2=0\%$) but lower incidence of motor block (OR = 4.05; 95% CI, 2.19–7.48, $I^2=60\%$) and pruritus (OR = 0.07; 95% CI, 0.03–0.16, $I^2=2\%$) in low concentration groups. Nevertheless, the methods in maintenance of epidural labor analgesia in these studies are CEI with PCEA methods, and unfortunately, we do not find studies available on this topic relate to PIEB techniques. The results of Shatalin et al. [29] demonstrated no advantage in using concentrated solutions in PIEB because of increased consumption of local anesthetic; however, they just compared their results with their previous studies so the conclusion was not convincing enough.

The risk and practical concern with PIEB

The main concern of the implementation of PIEB is that the optimal regimen of PIEB remains unknown. In addition, different institutions use different types and concentrations of drugs, and each patient has their own conditions (such as weight, height, progression of labor, and the condition of the epidural space). Therefore, adjustments to the PIEB plan must be made for each individual patient. Due to the larger boluses and longer interval of PIEB administration compared with CEI, complications such as subarachnoid blockage, drug entry into the bloodstream, and catheter obstruction are difficult to detect in a timely manner. Therefore, right after the placement of the epidural catheter, experimental doses should be administered and attention should be paid to observe the blood pressure, heart rate and pain relief of the parturient after administering the loading dose. The administration plan also should be adjusted promptly according to these conditions. After the loading dose is administered, patients typically experience significant pain relief, reduced release of catecholamines, and increased uterine contractions. However, this may result in fetal head compression and bradycardia. Therefore, continuous fetal heart monitoring is necessary too. During labor analgesia, blood pressure, heart rate, and fetal heart rate should be continuously monitored to ensure safety and relevant personnel should always be nearby to promptly identify potential risks and improve patient discomfort.

The adjustment of PIEB parameters should be within the safe range, higher dose may increase the incidence of motor block and hypotension, short intervals may increase drug consumption and affect the setting of PCEA lockout time, and high flow rates may increase the incidence of high-pressure alarms. Thus, several parameters should be adjusted together rather than adjusting a single parameter.

Due to the shortage of anesthesiologists in China, they cannot always stay with the parturient. Therefore, training should also be provided to midwives and obstetricians, so that they can timely detect patients' discomfort or problems with the analgesic pump and inform the anesthesiologist in a timely manner. The price is also a factor that needs to be considered. As far as we know, the cost of PIEB pump is similar to that of CEI pump. Of course, institutions can also purchase pumps combined with PCEA or CEI to provide different choices for economically capable parturients.

Conclusion

PIEB as a new technique in maintenance of labor analgesia is advantageous and promising. From the current studies, it has the potential to improve analgesic quality and reduce consumption of narcotic compared with CEI and reduce the occurrence of breakthrough pain, motor block but increase the drug consumption compared with PCEA. Meanwhile, the incidence of side effects does not increase. The advantages of PIEB compared with CEI might be associated with a wider sensory block and better homogeneous distribution. The optimal regimen is still unclear. Anesthesiologists still need to formulate the implementation strategies according to the specific conditions of patients, medical institutions and the existing research results. The recent researches indicate that longer interval may decrease the body temperature and the incidence of postpartum fever with fewer anesthetics is used. Higher flow rate, higher gauged catheters, and wire-reinforced and multi-orifice catheters can generate higher pressure in vitro condition. Equipment may also affect analgesia by influencing the maximum pressure. In current clinical studies, no difference has found between the flow rate and analgesic quality. Lower concentrations of local anesthetics may have some benefits, but this still needs to be confirmed by the future studies. From the existing results, we think that using lower concentration anesthetic with the time interval in the range of 35–40 min, higher gauged, wire-reinforced, and multi-orifice catheters, lower than 250 ml/h flow rate can be a reference regimen. Besides, during the whole process, blood pressure, heart rate, and fetal heart rate should be continuously monitored and administration plan also needs to be adjusted promptly according to patient's condition.

Authors contribution PZ and FN contributed to the study conception and design. FN performed the literature search and data analysis. FN drafted and ZW critically revised the work. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The data of this work are available from the corresponding author upon reasonable request.

References

1. Hiltunen P, Raudaskoski T, Ebeling H, Moilanen I. Does pain relief during delivery decrease the risk of postnatal depression? Acta Obstet Gynecol Scand. 2004;83(3):257–61.
2. Shnider SM, Wright RG, Levinson G, Roizen MF, Wallis KL, Rolbin SH, Craft JB. Uterine blood flow and plasma norepinephrine changes during maternal stress in the pregnant ewe. Anesthesiology. 1979;50(6):524–7.

3. Sng BL, Zeng Y, de Souza NNA, Leong WL, Oh TT, Siddiqui FJ, Assam PN, Han NR, Chan ES, Sia AT. Automated mandatory bolus versus basal infusion for maintenance of epidural analgesia in labour. Cochrane Database Syst Rev. 2018;5:CD011344.
4. Lim G, Facco FL, Nathan N, Waters JH, Wong CA, Eltzschig HK. A review of the impact of obstetric anesthesia on maternal and neonatal outcomes. Anesthesiology. 2018;129(1):192–215.
5. Onuoha OC. Epidural Analgesia for Labor. Anesthesiol Clin. 2017;35(1):1–14.
6. Capogna G, Camorcia M, Stirparo S, Farcomeni A. 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(4):826–31.
7. Sia AT, Leo S, Ocampo CE. A randomised comparison of variable-frequency automated mandatory boluses with a basal infusion for patient-controlled epidural analgesia during labour and delivery. Anaesthesia. 2013;68(3):267–75.
8. Heesen M, Bohmer J, Klohr S, Hofmann T, Rossaint R, Straube S. The effect of adding a background infusion to patient-controlled epidural labor analgesia on labor, maternal, and neonatal outcomes: a systematic review and meta-analysis. Anesth Analg. 2015;121(1):149–58.
9. Ferrer LE, Romero DJ, Vasquez OI, Matute EC, Van de Velde M. Effect of programmed intermittent epidural boluses and continuous epidural infusion on labor analgesia and obstetric outcomes: a randomized controlled trial. Arch Gynecol Obstet. 2017;296(5):915–22.
10. 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(2):426–35.
11. Haidl F, Arne Rosseland L, Rorvik AM, Dahl V. Programmed intermittent boluses vs continuous epidural infusion in labor using an adrenaline containing solution: A randomized trial. Acta Anaesthesiol Scand. 2020;64(10):1505–12.
12. Riazanova OV, Alexandrovich YS, Guseva YV, Ioscovich AM. A randomized comparison of low dose ropivacaine programmed intermittent epidural bolus with continuous epidural infusion for labour analgesia. Rom J Anaesth Intensive Care. 2019;26(1):25–30.
13. Fan Y, Hou W, Feng S, Mao P, Wang X, Jiang J, Yuan H, Shen X, Feng S, Li P. Programmed intermittent epidural bolus decreases the incidence of intra-partum fever for labor analgesia in primiparous women: a randomized controlled study. Arch Gynecol Obstet. 2019;300(6):1551–7.
14. Xu J, Zhou J, Xiao H, Pan S, Liu J, Shang Y, Yao S. A systematic review and meta-analysis comparing programmed intermittent bolus and continuous infusion as the background infusion for parturient-controlled epidural analgesia. Sci Rep. 2019;9(1):2583.
15. Wang XX, Zhang XL, Zhang ZX, Xin ZQ, Guo HJ, Liu HY, Xiao J, Zhang YL, Yuan SZ. Programmed intermittent epidural bolus in parturients: a meta-analysis of randomized controlled trials. Medicine (Baltimore). 2022;101(5): e28742.
16. 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(2):432–7.
17. Lin Y, Li Q, Liu J, Yang R, Liu J. Comparison of continuous epidural infusion and programmed intermittent epidural bolus in labor analgesia. Ther Clin Risk Manag. 2016;12:1107–12.
18. Holgado CM, Girones A, Tapia N, De Molina-Fernandez MI, Anez C. 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(12):1277–86.
19. Liu X, Zhang H, Zhang H, Guo M, Gao Y, Du C. Intermittent epidural bolus versus continuous epidural infusions for labor analgesia: A meta-analysis of randomized controlled trials. PLoS ONE. 2020;15(6): e0234353.
20. Hogan Q. Distribution of solution in the epidural space: examination by cryomicrotome section. Reg Anesth Pain Med. 2002;27(2):150–6.
21. Mowat I, Tang R, Vaghadia H, Krebs C, Henderson WR, Sawka A. Epidural distribution of dye administered via an epidural catheter in a porcine model. Br J Anaesth. 2016;116(2):277–81.
22. Lim Y, Sia AT, Ocampo C. Automated regular boluses for epidural analgesia: a comparison with continuous infusion. Int J Obstet Anesth. 2005;14(4):305–9.
23. Roofthooft E, Barbe A, Schildermans J, Cromheecke S, Devroe S, Fieuws S, Rex S, Wong CA, Van de Velde M. Programmed intermittent epidural bolus vs. patient-controlled epidural analgesia for maintenance of labour analgesia: a two-centre, double-blind, randomised studydagger. Anaesthesia. 2020;75(12):1635–42.
24. Bourges J, Gakuba C, Plass F, Gerard JL, Simonet T, Hanouz JL. Effect of patient-controlled epidural analgesia with and without automatic intermittent bolus on levobupivacaine consumption during labour: A single-centre prospective double-blinded randomised controlled study. Anaesth Crit Care Pain Med. 2021;40(5): 100936.
25. Song Y, Du W, Zhou S, Zhou Y, Yu Y, Xu Z, Liu Z. 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(4):971–8.
26. 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(4):904–11.
27. Epsztein Kanczuk M, Barrett NM, Arzola C, Downey K, Ye XY, Carvalho JC. 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 mug/mL. Anesth Analg. 2017;124(2):537–41.
28. Bittencourt R, Arzola C, Zakus P, Downey K, Ye XY, Carvalho JCA. A biased coin up-and-down sequential allocation trial to determine the optimum programmed intermittent epidural bolus time interval between 5 mL boluses of bupivacaine 0.125% with fentanyl 2 microg.mL(-1). Can J Anaesth. 2019;66(9):1075–81.
29. Shatalin D, Arzola C, Downey K, Ye XY, Carvalho JCA. Programmed intermittent epidural bolus for labour analgesia during first stage of labour: a sequential allocation trial to determine the effective interval time between boluses of a fixed volume of 2.5 mL of bupivacaine 0.25% plus fentanyl 8 microg.mL(-1). Can J Anaesth. 2021;68(5):653–60.
30. Zhou SQ, Wang J, Du WJ, Song YJ, Xu ZD, Liu ZQ. Optimum interval time of programmed intermittent epidural bolus of ropivacaine 0.08% with sufentanyl 0.3 mug/mL for labor analgesia: a biased-coin up-and-down sequential allocation trial. Chin Med J (Engl). 2020;133(5):517–22.
31. Li B, Yuan S, Chen A, Ma D, Fu W. Programmed intermittent epidural bolus at different intervals combined with patient-controlled epidural analgesia on body temperature during labour analgesia. J Coll Physicians Surg Pak. 2020;30(5):463–6.
32. Krawczyk P, Piwowar P, Salapa K, Lonc T, Andres J. Do epidural catheter size and flow rate affect bolus injection pressure in different programmed intermittent epidural bolus regimens? An In Vitro Study Anesth Analg. 2019;129(6):1587–94.

33. Klumpner TT, Lange EM, Ahmed HS, Fitzgerald PC, Wong CA, Toledo P. An in vitro evaluation of the pressure generated during programmed intermittent epidural bolus injection at varying infusion delivery speeds. J Clin Anesth. 2016;34:632–7.
34. Lange EMS, Wong CA, Fitzgerald PC, Davila WF, Rao S, McCarthy RJ, Toledo P. Effect of epidural infusion bolus delivery rate on the duration of labor analgesia: a randomized clinical trial. Anesthesiology. 2018;128(4):745–53.
35. Mazda Y, Arzola C, Downey K, Ye XY, Carvalho JCA. Programmed intermittent epidural bolus for labour analgesia: a randomized controlled trial comparing bolus delivery speeds of 125 mL.hr(-1) versus 250 mL.hr(-1). Can J Anaesth. 2022;69(1):86–96.
36. Sultan P, Murphy C, Halpern S, Carvalho B. The effect of low concentrations versus high concentrations of local anesthetics for labour analgesia on obstetric and anesthetic outcomes: a meta-analysis. Can J Anaesth. 2013;60(9):840–54.
37. Zhang L, Hu Y, Wu X, Zhang X. A systematic review and meta-analysis of randomized controlled trials of labor epidural analgesia using moderately high concentrations of plain local anesthetics versus low concentrations of local anesthetics with opioids. J Pain Res. 2021;14:1303–13.