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Programmed intermittent epidural boluses (PIEB) in labor analgesia : a narrative review of the present

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Abstract: *Purpose*: The programmed intermittent epidural bolus (PIEB) technique is a promising technique for maintenance of analgesia during labor. The use of this technique may offer multiple benefits over the current traditional and conventional maintenance modes such as continuous epidural infusion (CEI) and patient controlled epidural analgesia (PCEA). The goal of the present review of the literature is to summarize the current literature on the use of PIEB for labor analgesia.
Findings: From a total of 49 identified articles, 35 were included in the review. In this review we discuss the mechanism of PIEB, the current literature comparing PIEB to CEI and the ideal pump settings. PIEB, as a new analgesia maintenance technique, remains a focus of interest and intensive research with the potential to further optimize labor analgesia. When comparing PIEB technique to continuous epidural infusion (CEI), studies show a dose reduction of local anesthetic and opioid consumption, a reduction in breakthrough pain, an improvement of maternal satisfaction and a reduction of the incidence of motor block. Recently, efforts are made to refine the optimal settings for bolus dosing, time intervals and frequency for epidural analgesia with the hope to further improve safety, efficacy and patient satisfaction in the future. Further research however is needed to determine the optimal volume, flow rate, time interval and drug concentration for PIEB for labor analgesia.
Summary: We examined the recent progress and refinements of PIEB and evaluated the potential of this technique to improve safety, efficacy and maternal satisfaction during labor.

Key words : PIEB, programmed intermittent epidural bolus, AMB, automated mandatory bolus, epidural, labor analgesia, maintenance of labor analgesia, CIB, continuous intermittent bolus

Introduction

Labor pain is a dynamic and complex experience. It is subjective and personal in nature and generally considered as one of the most painful experiences that women can encounter. Severe pain experienced during labor may have long term consequences such as postpartum depression, chronic pain and psychological vulnerability (1, 2). Effective labor epidural analgesia depends on the effective distribution and absorption of the administered analgesic solution, usually a local anesthetic with or without an opioid solution, from and within the epidural space into the cerebrospinal fluid (3). Neuraxial labor analgesia, such as combined spinal epidural anesthesia (CSE) and epidural analgesia are the most effective and most commonly utilized methods for pain relief during labor and are considered as golden standard (1). Following an initial spinal or epidural loading dose, analgesia is maintained by the administration of the analgesic solution through an epidural catheter. In the past, maintenance of labor analgesia was accomplished by manual and repetitive intermittent boluses by the anesthesiologist or midwife. This method depends on the response of the parturient when anesthesia decreases and pain returns. With the development of infusion pumps, the maintenance of labor analgesia by a continuous epidural infusion was made possible to prevent pain re-occurrence. This improvement led to more consistent analgesia, higher patient satisfaction and a reduction of clinician interventions and workload for the anesthesiologist. Often the possibility of patient controlled epidural analgesia (PCEA) for breakthrough pain was added to a continuous epidural infusion (CEI) technique to improve analgesia and reduce the need for clinician

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Table 1

Setting	Definition		Advantages	Disadvantages
CEI	Continuous Epidural Infusion	Continuous infusion of analgesic solution delivered at a continuous rate.	-Consistent analgesia -Less clinician interventions	-Motor block -High LA consumption -More instrumental deliveries
CEI + PCEA	Continuous Epidural Infusion + Patient Controlled Epidural Analgesia	Continuous infusion of analgesic solution delivered at a continuous rate with additional intermittent boluses of an analgesic solution initiated by the patient within programmed lock-out interval times.	-Less breakthrough pain -Consistent analgesia -Less clinician interventions	-Motor block -High LA consumption -More instrumental deliveries
PIEB	Programmed Intermittent Epidural Boluses	Intermittent boluses of an analgesic solution administered by a programmed infusion pump at programmable intervals.	-Consistent analgesia -Less clinician interventions -Lower LA consumption -Less motor block	-Pump technology needed
PIEB + PCEA	Programmed Intermittent Epidural Boluses + Patient Controlled Epidural Analgesia	Intermittent boluses of an analgesic solution administered by a programmed infusion pump at programmable intervals with additional intermittent boluses of an analgesic solution initiated by the patient within programmed lock-out interval times.	-Consistent analgesia -Less clinician interventions -Lower LA consumption -Less motor block	-Pump technology needed
PCEA	Patient Controlled Epidural Analgesia	Intermittent boluses of an analgesic solution initiated by the patient within programmed lock-out interval times.	-Self administration and self control -Lower LA consumption	-Inconsistent analgesia -Patient education needed

boluses. Although theoretically more consistent analgesia is provided with this continuous infusion technique, local anesthetic consumption and the incidence of motor blockade, contributing to increased rates of instrumental deliveries and shoulder dystocia, are higher compared to bolus administration techniques. Continuous infusion also tends to result in progressive regression of the block, with failure of pain control and breakthrough pain and increase in physician workload. So both PCEA and CEI techniques do not eliminate the need for clinician boluses for breakthrough pain (2, 4, 5, 6) (Table 1).

Recently the PIEB technique has been proposed as an alternative mode of maintenance by several studies. Programmed intermittent boluses have the potential benefit of providing a consistent level of analgesia and minimizing physician rescue workload (7). However CEI with or without PCEA remained the traditional practice in most centers as a result of the absence of pump technology to deliver a preset intermittent epidural bolus with PCEA. In recent years this pump technology has become available.

The programmed intermittent epidural bolus technique or automated mandatory bolus technique (AMB) uses a programmed infusion pump to administer intermittent boluses of an analgesic solution at programmable intervals to maintain labor analgesia. It can be used as an alternative to CEI alone or as a background administration with PCEA. This technique combines the advantages of manual boluses and continuous infusion resulting in effective labor analgesia without physician intervention but with a better epidural spread than when a continuous infusion is given (4).

PIEB is suggested to be a superior mode for the maintenance of labor epidural analgesia compared to a conventional CEI. Literature found better or equal analgesia quality with reduced local anesthetic consumption, fewer and later PCEA boluses, less motor blockade with a lower incidence of instrumental vaginal delivery, greater maternal satisfaction scores, shorter second stage labor times and less anesthesia interventions with PIEB compared to CEI (3, 5, 6, 12, 16, 19-24, 26-29).

The motivation behind the PIEB technique is that delivering the basal local anesthetic solution as regularly spaced, intermittent boluses may provide improved analgesia with a lower drug dose than compared with CEI. The exact mechanism, however, is not fully understood. The benefits of PIEB can potentially be explained by the higher volume and injection pressure with boluses where they are more likely to produce a uniform diffusion and a greater spread of the analgesic solution within the epidural space as shown in cadaveric dissections (8). Probably not only the peak pressures but also the method of delivering the bolus influences the dynamics of the nerve block resulting in a better distribution (4). Additionally, in an in vitro model, when using multi-orifice epidural catheters, continuous infusion with lower injection pressures results only in flow through the proximal hole while

higher injection pressures via a manual bolus result in better flow through all catheter ports leading to greater spread resulting in lower intraneural anesthetic concentrations (1, 3, 6). Multi-orifice catheters are proven to be superior over single-orifice catheters for labor analgesia (9).

Analgesia and motor block are both produced by the diffusion of local anesthetics from the extraneural space into the nerve. After a single bolus administration, the initial concentration is greater outside of the nerve fiber, but over time, the extraneural concentration equals the intraneural concentration, establishing a steady state. Nerve blockade is eventually overcome when the intra-neural concentration exceeds the extraneural concentration and the diffusion gradient is reversed. In PIEB, the intermittent boluses assure that the amount of LA inside the nerve fiber is sufficient to block the small outer sensory fibers, but not the thicker inner motor fibers. In case of continuous infusion, the extraneural concentration is generally constantly higher than in the intraneural space, and the total concentration inside the nerve is therefore increased over time and may reach the threshold for motor block, even when low concentration of local anesthetics are used (10).

The better distribution of local anesthetics with PIEB can result in superior analgesia and in lower intraneural anesthetic concentrations in the epidural space. As a result of these lower intraneural LA concentrations, less neuronal motor fibers will be blocked with decreased motor block in comparison to continuous infusion (2,6). Because excessive motor block potentially reduces pelvic muscle tone, it can lead to difficulties in internal rotation of the fetal head resulting in an increased risk of instrumental delivery (4, 11).

This is in contrast to CEI where continuous infusion tends to result in progressive regression of the block, with failure of pain control and breakthrough pain. Compared to CEI, PIEB can therefore reduce the anesthetic workload by providing more consistent analgesia throughout labor. This finding can be a great advantage in a busy maternity ward.

The benefits of PIEB over CEI are proven to be more significant in patients with labor of longer duration. Therefore, women undergoing induction of labor and nulliparous women benefit the most (12).

The current review article is a focused narrative review of the literature published on programmed intermittent epidural boluses. A comprehensive search of the literature published on PIEB was performed using the Pubmed and Cochrane databases using the following search terms: PIEB, programmed intermittent epidural bolus, AMB, automated mandatory bolus, epidural, labor analgesia, maintenance of labor analgesia, CIB, continuous intermittent bolus. Our search was concentrated on randomized control trials (RCTs), systematic reviews and meta-analysis of RCTs as well as observational trials. From a total of 49 identified articles after detailed consideration, we agreed to include 35 articles in the review.

Results

PIEB vs CEI

Since 2005, RCTs have compared the effects of delivering the epidural analgesic solution via PIEB versus the standard delivery mode of CEI with or without PCEA. Because there was no commercially available pump capable of delivering PIEB with PCEA, non-commercial prototypes were used and showed the benefits of PIEB compared to CEI. Most studies even used a 2-pump system per patient, which may not be comparable to a single pump system with the possibility to deliver both modes. Despite previous observations on PIEB, continuous infusions remained standard, primarily because in most centers the infusion pumps were only able to deliver a continuous infusion. Recently, more sophisticated devices are available and allowed re-evaluation of programmed bolus administration at regular intervals. In 2014, the CADD-Solis PIB Ambulatory Infusion System received FDA approval. With these pumps, various settings are available and must be determined: (1) the interval between spinal dose and first PIEB, (2) the interval time between PIEB, (3) the volume of PIEB, (4) the volume of PCEA bolus, (5) the flow at which PIEB and PCEA boluses are delivered and (6) the interaction or lock-out between PIEB and PCEA boluses. The interaction between PIEB and PCEA can be set up in two different ways, either using the interval time between PIEB or the interval time between the PCEA boluses. (3) With the old software, a maximum flow rate of 175 mL/h was possible. The new software allows for rates up to 250mL/h with standard tubing and even up to 500mL/h with special high-flow tubing (6). The mechanisms explaining the proposed improved spread of epidural solutions with the CADD-Solis PIB Ambulatory Infusion System remain to be fully explored. An in-vitro study showed that the delivery of programmed boluses with the CADD-Solis PIB

Table 2

Study	Date	Patients	Initiation	PCEA	Solution	Catheter	Pump	CEI	PIEB	Outcome	Ref
CHUA	2004	42 nulliparous	CSE: 25ug fentanyl plus lidocaine 1.5% 3 mL epidural test dose	-	ropivacaïne 0.1% plus fentanyl 2 **µg**/mL	Multi-orifice	-Graseby 9200 pump -Terumo syringe pump	5 mL/h immediately	30 min. post-induction, 5 mL every 60 min.	longer analgesia, lower VAS scores, higher sensory block	19
LIM	2005	60 parturients	CSE: fentanyl 25 µg	-	Levobupivacaïne 0.1% plus fentanyl 2 µg/mL	Multi-orifice catheter	-Rythmic™ Pump Micrel Medical Devices -Terumo pump	10 mL/h immediately	15 min. post-induction, 5 mL every 30 min.	Less breakthrough pain, greater patient satisfaction	16
FETTES	2006	40 primigravida	Epidural: 15-20 mL ropivacaïne 0.2%	-	ropivacaïne 0.2% plus fentanyl 2 **µg**/mL	Three side hole catheter	Medfusion 2001	10 mL/h immediately	30 min. post- induction, 10 mL every 60 min.	less PATU, reduced LA consumption, longer time to PATU	20
WONG	2006	126 parous	CSE: bupivacaine 1.25 mg plus fentanyl 15 µg and epidural test dose 3 mL lidocaine 1.5% with epinephrine 1:200000	bupivacaine 0.625 mg/mL and fentanyl 2 **µg**/mL, 5 mL, lock-out 10 min.	bupivacaine 0.625 mg/mL plus fentanyl 2 **µg**/mL	Single-orifice catheter	2 CMS 4000 pumps	12mL/h 15 min.after induction	6mL bolus every 30 min., 45 min. after induction	reduced LA consumption, less PATU, greater patient satisfaction	12
SIA	2007-2010	42 nulliparous - 62 nulliparous	CSE: ropivacaïne 2 mg plus fentanyl 15 µg	5 mL, lock-out 10 min.	ropivacaïne 0.1% plus fentanyl 2 **µg**/mL	Multi-orifice catheter	IVAC P700 - Perfusor® Compact S infusion pump	5mL/h immediately	30 min. post- induction, 5 mL every 60 min.	reduced LA consumption, longer time to PCEA, less patients needing PCEA, greater patient satisfaction	21-22
LIM	2010	50 pregnant	CSE: ropivacaïne 2 mg plus fentanyl 15 µg	-	Ropivacaïne 0.1% plus fentanyl 2 **µg**/mL	Multi-orifice catheter	-Rythmic™ Pump Micrel Medical Devices -Infusion Pump Syringe Terumo TE 311	10 mL/h, immediately	7.5 min. post- induction, 2.5 ml every 15 min.	no differences	23
LEO	2010	62 nulliparous	CSE: ropivacaïne 2 mg plus fentanyl 15 **µg** and an lidocaine 1.5% 3 mL test dose	5 mL, lock-out 10 min.	ropivacaïne 0.1% plus fentanyl 2 µg/mL	Multi-orifice catheter	IVAC P700 and later a modified Perfusor Compact S infusion pump	5 mL/h immediately	30 min. post- induction, 5 mL every 60 min.	greater patient satisfaction, longer duration of analgesia, reduced LA c consumption	22
CAPOGNA	2011	145 nulliparous	Epidural: 20 mL levobupivacaïne 0.0625% plus sufentanil 0.5 **µg**/mL	levobupivacaïne 0.125%, 5 mL, lock-out 10 min.	levobupivacaïne 0.0625% plus sufentanil 0.5 **µg**/mL	Multi orifice catheter	2 Gemstar Hospira pumps	10 mL/h immediately	60 min. post- induction, 10 mL every 60 min.	reduced LA consumption, less patients needing PCEA, lower number of PCEA per patient, less motor block, less instrumental delivery	24
NUNES	2016	106 pregnant	Epidural: 10 mL with ropivacaïne 0.16% plus Sufentanil 10µg	5 mL	Ropivacaïne 0.15% plus Sufentanil 0.2 µg/mL (1) and ropivacaïne 0.1% plus Sufentanil 0.2 µg/Ml (2)	Multi-orifice catheter	N/A	5 mL/h immediately (1)	10 mL every 60 min., 60 min. post-induction (1) and (2)	reduced incidence of cesarean delivery	27

MCKENZIE	2016	709 pregnant	Epidural: 15 mL 0.125% bupivacaine with sufentanil 10 mg or CSE: bupivacaine 2.5 mg plus sufentanil 5 mg	12 mL, lock-out 15 min. (3) or 10 mL, lock-out 10 min. (4)	0.0625% bupivacaine plus sufentanil 0.4 mg/mL	Single orifice catheter	N/A	12 mL/h immediately (3)	30 min. after induction, 9 mL every 45 min. (4)	less rescue boluses	5
TIEN	2016	528 pregnant	CSE: bupivacaine 1.25-2.5 mg plus fentanyl 10-15 µg or epidural: bupivacaine 15-20 mg plus fentanyl 50 µg	5 mL, lock-out 8 min.	bupivacaine 0.125 mg/mL plus fentanyl 2 µg/mL	N/A	CADD-Solis v3.0 pump	5 mL/h, immediately	45 min. post- induction, 5 mL every 60 min. and 45 min. post-induction, 3 mL every 30 min.	no differences	6
LIN	2016	200 nulliparous	Epidural: ropivacaine 0.15% 10 mL	5 mL, lock-out 20 min.	ropivacaine 0.1% plus sufentanil 0.3 µg/mL	N/A	N/A	5 mL/h	5 mL every 60 min.	better VAS scores and lower LA consumption	26
LEONE	2016	104 second trimester TOP	Epidural: 20 mL levobupivacaine 0.0625% with sufentanil 10 **µg**	-	levobupivacaine 0.0625% plus sufentanil 0.5 **µg**/mL	Multi orifice catheter	N/A	10 mL/h 60 min. post-induction	60 min. post- induction, 10 mL every 60 min.	less motor block, greater patient satisfaction, less nausea	28
FERRER	2017	132 laboring	Epidural: 10 mL bupivacaine 0.1%	-	bupivacaine 0.1% plus fentanyl 2 µg/mL	N/A	Sapphire pump	10 mL/h immediately	60 min. post- induction, 10 mL every 60 min.	reduced LA consumption	29
DELGADO	2018		CSE	+	bupivacaine 0.0625% with fentanyl 2 **µg**/mL	Single orifice catheter	Cadd Solis	10 mL/h	PIEB45: 10 mL every 45 min. PIEB60: 10 mL/h every 60 min. PIEB45HF: 10 mL/h every 45 min. using a high flow delivery system (500 mL/h)	no differences	3

Ambulatory Infusion System uses a peristaltic movement with a consistently higher pressure than the continuous infusion, although it is still not clear whether it is the peak pressure or the intermittent mode of delivery which results in the better epidural spread (13). There are no human cadaver studies yet confirming this hypothesis, however, a study on pigs demonstrated greater segmental dye spread when comparing single boluses with short continuous infusions (14). Studies using a single pump to evaluate the efficacy and superiority of PIEB technique are very limited. New randomized prospective studies with a single pump are needed to clarify the effect of different flow rates and settings compared to old pumps and to verify that the outcomes are similar independently from the pump settings (15).

PCEA

PCEA is a top-up technique in which the patient has the possibility to self-administer a bolus of epidural solution at irregular intervals with programmed lock-out periods. With this method the patient can administer a bolus when analgesia wanes and labor pain returns. (4) It has proved to decrease breakthrough pain requiring physician's top-ups, reduce local anesthetic consumption and increase patient satisfaction without compromising analgesic efficacy (16). Recent studies investigating the optimal technique for maintaining epidural labor analgesia have incorporated the use of PCEA for additional analgesia. PCEA was mostly used in addition to PIEB or CEI to defeat breakthrough pain. Halpern et Carvalho compared 7 RCTs on PCEA with and without background infusions. Although lower local anesthetic consumption was reported in women receiving PCEA alone, none of the other outcomes were significantly different in patients who received PCEA without basal infusion (17). Even though Sezer and Gunaydin demonstrated that PCEA only technique provided satisfactory maintenance analgesia, there has been no consensus on the use of this mode as an adequate and optimal maintenance analgesic regimen for labor (18). More studies should be carried out in order to confirm the superiority of PIEB/PCEA compared with PCEA only as an intermittent bolus technique itself.

Current evidence and literature review

Several studies (Table 2) compared PIEB with or without PCEA with the CEI with or without PCEA technique for labor analgesia. Most studies

analyzed differences in pain scores, local anesthetic consumption, motor blockade, duration of labor, mode of delivery and maternal satisfaction. In general, despite heterogeneous methodology they concluded that the automated bolus technique is superior to the CEI technique providing either equal or better analgesia with less drug consumption. Higher maternal satisfaction scores, decreased motor blockade and, consequently, lower instrumental delivery have also been associated with this maintenance technique. We listed a brief overview of the studies performed on PIEB since 2004. These studies include RCTs, meta-analyses and retrospective reviews.

In 2004 Chua and Sia randomized 42 patients and compared intermittent bolus technique with CEI after initiation with CSE analgesia in a randomized, double blind controlled trial. The intermittent bolus group had a longer duration of uninterrupted analgesia after the initiation of CSE analgesia, lower pain scores and a higher sensory block compared with the CEI group. (19) Lim et al. recruited 60 parturients into a randomized controlled trial in 2016. After a CSE was performed the parturients were randomly allocated into two groups. The CEI group received a solution of levobupivacaïne 0.1% plus fentanyl 2 µg/mL at a rate of 10 mL/h. The PIEB group received a 5mL epidural boluses every 30 minutes. The bolus group showed a lower incidence of breakthrough pain compared to the infusion group and satisfaction scores in the PIEB group were significantly higher (16). In 2006 Wong et al. carried out a prospective, randomized, double-blind study on 126 multiparous women undergoing induction of labor who requested CSE analgesia. The patients were randomized to receive either PIEB (6mL bolus every 30 minutes, 45 minutes after induction) or CEI (12 mL/h, 15 minutes after induction) with a bupivacaine and fentanyl solution. In both groups PCEA boluses were available using a dual pump system. Their primary outcome variable was total bupivacaine consumption per hour of infusion. Their results showed that the maintenance of epidural analgesia was similar in both groups, but PIEB with PCEA used a smaller bupivacaine dose, required fewer PATU and had greater patient satisfaction. These differences were greater in subjects with labor of longer duration. We must note a high incidence of breakthrough pain requiring PATU in which the same concentration of local anesthetic was used (12). In the same year Fettes et al. recruited 40 primigravidas into a randomized, double-blind controlled trial. Epidural analgesia was initiated and the parturients were randomized into a group receiving a CEI of ropivacaïne with fentanyl at 10 mL/h or one receiving hourly boluses of 10 mL of the same solution without PCEA. The study was designed to measure the efficacy of analgesia during the first stage of labor. Their results showed that the use of regular intermittent epidural injections was associated with a lower requirement for epidural rescue medication, lower total epidural drug consumption and longer time to first rescue bolus for breakthrough pain while providing equivalent pain relief compared with a continuous infusion. However, pain scores, sensory spread and motor block were similar in both groups (20). In 2007 Sia et al. randomized 42 parturients following a CSE induction into two groups using a single pump system. One group received CEI with PCEA and the second group received PIEB with PCEA. The second group showed reduced overall consumption of ropivacaïne, longer analgesia before the first PCEA bolus and a smaller proportion of patients who required a PCEA bolus. There was however, no difference in the need for clinician interventions. In a follow-up study in 2010, 62 patients were randomized to receive either CEI with PCEA or PIEB with PCEA using a modified version of the original algorithm. Almost identical findings to the first study were noted (21, 22). Another study of Lim et al. in 2010 randomized 50 parturients to receive either CEI of 10 mL/h or automated intermittent boluses of 2.5mL every 15 minutes all receiving a ropivacaïne 0.1% solution with fentanyl 2 µg/mL. The results demonstrated that breakthrough pain was comparable in both groups (23). Also in 2010 Leo et al. recruited 62 nulliparous women for their study. Labor pain was initiated with the CSE technique. After a spinal loading dose, with ropivacaïne 2mg and fentanyl 15µg and an epidural catheter flush with 3mL of lidocaine 1.5%, subjects were randomized to receive ropivacaïne 0.1% with fentanyl 2µg/mL in a continuous infusion with PCEA or with automated mandatory boluses. Their primary outcome parameter was breakthrough pain and their secondary variables included local anesthetic consumption, maternal satisfaction scores and duration of effective labor analgesia. They failed to show any difference in the incidence of breakthrough pain requiring physician epidural top-up in both groups. However, patients in the PIEB group had greater satisfaction scores, longer duration of analgesia and reduced analgesic consumption (22). One year later, in 2011, Capogna et al carried out a randomized study in 145 nulliparous women receiving PIEB with PCEA or

CEI with PCEA. After an initial epidural loading dose of 20 mL levobupivacaïne 0.0625% with sufentanil 0.5 **µg**/mL, patients were randomized into two groups. The PIEB group received a 10 mL bolus of the same analgesic solution starting 60 minutes after the induction of analgesia. The CEI group received a 10mL/h infusion starting immediately after the epidural loading dose. Both regimens were supplemented by a PCEA pump using levobupivacaïne 0.125%. Pain scores and duration of labor analgesia did not differ between groups. But, there was significantly less total levobupivacaïne consumption, fewer patients needed PCEA boluses and there were lower number of PCEA boluses per patient in the PIEB group. Their most important finding was a lower incidence of motor block and instrumental delivery with PIEB. However, there was no difference in the caesarean delivery rate between the groups. This is the only study that reported lower instrumental delivery rates. The use of a more concentrated epidural solution than is often seen in routine clinical practice may have contributed to a higher rate of motor block in the CEI group (24). In 2013 George et al. including nine RCTs with low risk of bias involving 694 subjects published a meta-analysis of RCTs. Based on the hypothesis that CEI involves higher doses of local anesthetics resulting in motor blockade and subsequent instrumental deliveries, their primary outcome parameters were subject satisfaction, the need for manual anesthesia interventions, labor progression and the mode of delivery. Patients randomized to receive PIEB demonstrated reduced local anesthetic consumption, shorter second stage of labor and higher maternal satisfaction. They also suggest that PIEB may reduce instrumental delivery and reduce PATU. The investigators remarked that the pooled data for instrumental delivery rate, rate of anesthetic interventions and duration of labor had wide a confidence interval that contained clinically significant end points, therefore prohibiting definitive conclusions (25, 15). Mc Kenzie et al. in 2016 conducted a retrospective review of documented medical records for vaginal deliveries with neuraxial analgesia before and after the introduction of PIEB at their institution. In all cases labor analgesia was initiated with either 15 mL of epidural 0.125% bupivacaine with sufentanil 10 mg or CSE with intrathecal bupivacaine 2.5 mg with sufentanil 5 mg. Labor analgesia maintenance existed of CEI or PIEB. Their primary outcome parameter was the proportion of women requiring a clinician rescue bolus during labor. Results showed a significant difference in the primary outcome measure with fewer women in the PIEB group requiring a clinician rescue bolus during labor while providing comparable labor analgesia as CEI (5). In the same year, Tien et al. performed a retrospective comparison of 528 subjects from an academic university medical center who received maintenance of epidural labor analgesia via PIEB or CEI using the CADD-Solis v3.0 pump. Their aim was to assess whether the use of PIEB is associated with decreased local anesthetic consumption, decreased PCEA use, and decreased rescue analgesia requirements compared with CEI. The neuraxial regimen used to initiate labor analgesia with CSE. All subjects were categorized into 3 groups: CEI 5 mL per hour, PIEB 5 mL per 60 minutes and PIEB 3 mL per 30 minutes with similar PCEA settings. The primary outcome parameter was the total volume of local anesthetics consumed per hour. Secondary outcome measures were need for clinician boluses, PCEA use, motor blockade, and delivery mode. They had to conclude that through this retrospective study the epidural maintenance regimen used was not associated with differences in local anesthetic consumption, delivery mode, and motor blockade. We have to note the limitations of this study being single center, retrospective without randomization (6). Lin et al. conducted a study with the aims to investigate differences between CEI and PIEB analgesia in 200 nulliparous women. After epidural initiation, patients were randomized to receive a ropivacaïne 0.1% with sufentanil 0.3 µg/mL solution either as a CEI at a rate of 5 mL/h combined with PCEA 5 mL or as PIEB of 5 mL with PCEA 5 mL. The lockout interval for PCEA boluses was 20 minutes in both groups. There was no difference in demographic characteristics, duration of first and second stages, delivery methods, sensory block, fetal Apgar scores, and the maternal outcomes between the CEI and IEB groups. There was a significant difference in VAS scores and epidural ropivacaïne total consumption between the two groups (26). Nunes et al. performed a prospective, randomized, blinded-endpoint, controlled study in 130 laboring women. After an epidural loading dose, parturients were randomly assigned to one of three regimens: CEI 5mL/h with ropivacaïne 0.15% with sufentanil 0.2 µg/mL, PIEB 10 mL with ropivacaïne 0.1% plus sufentanil 0.2µg/mL and a second PIEB group with same solution as the CEI group. Rescue boluses of 5mL were available. They evaluated maternal satisfaction and adverse maternal and neonatal outcomes. Their conclusion was that maintenance of epidural analgesia with programmed intermittent

epidural bolus was associated with a reduced incidence of caesarean delivery with equal maternal satisfaction and no adverse outcomes (27). Leone et al. designed a randomized double blind control trial in women for second trimester termination of pregnancy. 102 women were randomly assigned to receive continuous epidural infusion or programmed intermittent epidural bolus. They found that for second trimester TOP, compared with CEI, a PIEB technique was associated with a lower incidence of motor block, less nausea and greater patient satisfaction while analgesia was similar in both groups (28). McKenzie et al. conducted a retrospective analysis after changing from a CEI protocol to PIEB for labor analgesia with PCEA. The CEI settings were 12mL/h with PCEA and the new PIEB settings were a 9 mL bolus every 45min with PCEA. Medical records were compared and they saw fewer patients in the PIEB group requiring rescue clinician boluses compared to the CEI group with comparable labor analgesia (5). In 2017 Ferrer et al. designed an prospective randomized controlled single blind and parallel clinical trial in laboring women in an attempt to overcome the limitations such as the use of non-commercial PIEB pumps or manual intermittent epidural boluses that were seen in previous RCTs. Primary outcome was quality of analgesia. 132 women were randomized to epidural analgesia of 10 mL of a mixture of 0.1% bupivacaine plus 2 µg/mL of fentanyl either by programmed intermittent boluses or continuous infusion. Their study evidenced a lower anesthetic consumption in the programmed intermittent boluses group with similar labor analgesic control, and obstetric and newborn outcomes in both groups (29). Finally Delgado et al. in 2018 performed a 'before and after'-study to evaluate the analgesic effects of the two delivery options: PIEB and CEI, both with PCEA. They hypothesized that fewer physician administered top-ups would be administered in women receiving PIEB at different settings than among the CEI group with an equal hourly administration of analgesic solution delivered with a CADD-Solis pump. In this prospective observational study, the CEI group received bupivacaine 0.0625% with fentanyl 2 µg/mL at 10 mL/h with PCEA (5 mL bolus, 10 minute lock-out), whereas the PIEB groups received a programmed epidural bolus of 10 mL: every 45 minutes (PIEB45), every 60 minutes (PIEB60) and every 45 minutes using a high flow delivery system (500 mL/h) (PIEB45HF) with the same PCEA settings. Contrary to their expectations, they found no difference in the proportion of women requesting physician-administered top-ups between CEI and PIEB60 groups. The number of women requesting a PATU was lowest with the PIEB45 and PIEB45HF settings. They did not report PCEA data so it is possible that differences in PCEA use between groups have masked or prevented differences in PATU. (3)

The PIEB lock-out periods, bolus volumes and analgesia solutions vary significantly among studies <sinvestigating PIEB for maintenance of labor analgesia. The ideal combination is not known yet. In the previous studies we also see a wide variation in induction of analgesia, the use of PCEA, catheter choice, pump technology and patient population. Most studies are done on nulliparous women, while few have been done on multiparous women. Even PIEB regimens differ significantly among studies. The PIEB bolus size and interval, start time delay period and PCEA bolus size, interval and lockout time can influence the efficacy of PIEB used for labor analgesia. In order to optimize PIEB, additional adequately powered randomized controlled or prospective studies with standardized drug volume, dose, and concentrations are needed. The goal is to minimize the variety of results experienced when studying the different outcome measures (6, 7).

However, despite these diverse drug administration parameters, the majority of PIEB studies found decreased local anesthetic consumption, improved maternal satisfaction scores, decreased duration of labor and decreased numbers of clinician rescue boluses in PIEB groups compared to CEI without affecting pain scores during labor.

Pump settings

The optimal regimen for PIEB still remains to be determined. Recent studies have concentrated on optimizing the volume, frequency and patients demand feedback in epidural delivery. The optimal time interval and bolus dose regimen may depend on several factors, including the duration of labor, the concentration and specific components of the epidural solution and the rate of administration of the programmed bolus dose (15). Rates of the programmed bolus administration in the reviewed articles ranged from 75 – 400mL per hour. Wong et al. aimed to quantify the most optimal settings for injection volume and lockout interval for maintenance of epidural labor analgesia. After initiation of labor analgesia with a CSE technique they randomized 120 nulliparous parturients into one of three PIEB regimens for maintenance in which the bolus time interval and bolus volume were

manipulated. The first group received 2.5 mL every 15 minutes, 5mL every 30 minutes or 10mL every 60 minutes. The consumption of bupivacaine and other analgesic outcomes were evaluated. The local anesthetic consumption was significantly reduced when the time interval between intermittent bolus and bolus volumes was increased from 15 to 60 minutes and from 2.5 to 10 mL without decreasing pain scores or satisfaction scores. There were also less PCEA requests or PATU and an increase in time to these doses (30). Epstzein Kanczuk et al. conducted a double-blind, sequential allocation trial with a biased-coin up down design to obtain the effective interval 90% for the PIEB regimen to provide analgesia for first stage of labor without the use of PCEA. The PIEB interval was set at 60 minutes for the first patient and according to the response of previous patient, at varying time intervals (60-50-40-30 minutes) for subsequent patients. They concluded that the optimal time interval for PIEB of 10 mL of bupivacaine 0.0625% with fentanyl 2 µg/mL is approximately 40 minutes to provide effective analgesia in 90% women during first stage of labor. This dose corresponds to an hourly consumption of 9.4 mg of bupivacaine. The PIEB30 interval patients were also found to have higher sensory and motor blocks indicating that the interval should not be less than 30 minutes (31). In a subsequent study, the same group used a similar study design to determine the optimum PIEB volume at a 40 minutes bolus interval, providing effective analgesia in 90% of women during the first stage of labor, without using PCEA. They showed that the optimal PIEB volume of bupivacaine 0.0625% with fentanyl 2 **µg**/mL at a fixed interval of 40 minutes was 11mL. The hourly consumption of bupivacaine was 10.3 mg, which is consistent with previous findings. They also found that a PIEB bolus of less than 10 mL to be ineffective in providing adequate analgesia and above that to be associated with higher sensory and motor block, without causing maternal side effects (32, 33).

Not only the volume and frequency of bolus delivery can be controlled but also the delivery speed of the boluses. It is not known whether the delivery speed of the bolus injection influences analgesia outcomes. In an in vitro observational study Klumpner et al. tried to determine the pressure generated by a programmed bolus at delivery speeds of 100, 175, 300 and 400 mL/h in different catheters. They found that bolus infusion delivery speeds were directly related to peak pressure. This finding can be interesting since in vitro studies showed an association between injection pressure and epidural spread. Yet there is no evidence to guide the choice of delivery speed to correlate with ideal spread and quality of labor analgesia (8, 11, 34). These findings indicate that further alternatives for optimization should be explored. The use of higher concentration solutions may lead to PIEB volume reduction, but with a potential increase in total local anesthetic consumption. Another option may be the use of increased PIEB flow rate, which should provide a more extensive spread of local anesthetic solution in the epidural space and possibly volume and dose reduction (35). There had been no major advances in the delivery of labor analgesia until the introduction of PIEB, but unfortunately the optimal regimen for PIEB still remains unknown. More studies should be performed to determine the ideal PIEB/PCEA regimen concerning pump settings and the dose and concentration of analgesic solutions. Therefore, additional adequately powered randomized controlled studies are needed to determine the optimal combination of volume, frequency of administration, flow rate, drug choice and drug concentration to maximize the benefits of the PIEB technique. (35)

Conclusion

Labor pain is dynamic and multifactorial. To optimize this experience for the parturients with beneficial fetal and maternal outcomes it is necessary to develop personalized analgesic regimens for each parturient. During the past years, investigators focused on optimizing the existing methods of delivering neuraxial analgesia in labor such as CSE, PCEA and low dose analgesic solutions. They have already greatly enhanced our ability to safely and effectively manage pain throughout labor. These methods have redefined the way epidural analgesia is delivered. (1) Recent advances in pump technology allowed us to even better individualize and optimize labor analgesia. The PIEB is a new analgesia maintenance technique. In general, despite heterogeneous methodology, PIEB seems superior to CEI providing equal or even better analgesia with lower local anesthetic consumption and higher maternal satisfaction scores. Maternal satisfaction measures overall satisfaction with care provided and is not equivalent to analgesia. Continuous and stable analgesia, sense of control, painless uterine contraction feeling, ability to walk, absence of numbness and motor block and ability to push are all important factors that determine maternal satisfaction (10). It is important to evaluate how innovations in PIEB technology can further improve childbirth outcomes and maternal experience.

Despite the promising results and numerous studies performed on the subject of PIEB there are still no definitive regimens that have shown to be the optimal to reduce breakthrough pain or clinically significant outcomes such as instrumental or caesarean delivery. More focused research is required to investigate the multiple regimens in order to optimize the analgesic efficacy and safety of clinically relevant anesthesia and obstetric outcomes (1, 2, 35).

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