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REPORTS OF ORIGINAL INVESTIGATIONS

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 μg·mL^{-1}

Une étude d'attribution séquentielle par intervalles croissants et décroissants avec tirage biaisé afin de déterminer l'intervalle de temps optimal entre des bolus périduraux de 5 mL de bupivacaïne 0,125 % avec 2 μg·mL^{-1} de fentanyl

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Abstract

Purpose *The optimal epidural mixtures and settings for programmed intermittent epidural bolus (PIEB) labour analgesia have yet to be determined. A previous study by our group demonstrated that 10 mL boluses of bupivacaine 0.0625% with fentanyl 2 μg·mL^{-1} administered every 40 min provided effective analgesia during the first stage of labour for 90% of women, without breakthrough pain. We wanted to determine the effective PIEB time interval of 5 mL boluses of bupivacaine 0.125% with fentanyl 2 μg·mL^{-1} under the same study circumstances, aiming at a future comparative study.*

Methods *This double-blind dose-finding study used the biased coin up-and-down sequential allocation method to determine the effective PIEB interval 90% (EI90) needed to provide effective analgesia without breakthrough pain during the first stage of labour. We used fixed 5 mL boluses of bupivacaine 0.125% with fentanyl 2 μg.mL^{-1} and studied time intervals of 60, 50, 40, and 30 min. The first patient was assigned an interval of 60 min and the remaining intervals were assigned as per the biased coin up-and-down method.*

Results *The estimated EI90 was 36.5 min (95% confidence interval [CI], 34.0 to 39.0) by the truncated Dixon and Mood method and 34.2 min (95% CI, 30.8 to 41.5) by the isotonic regression method. We found that 20/40 women had an upper sensory block to ice above T6, 34/40 women had no motor block, and no woman required treatment for hypotension.*

Conclusion *The EI90 between 5 mL boluses of bupivacaine 0.125% with fentanyl 2 μg·mL^{-1} during the first stage of labour is approximately 35 min.*

Trial registration *www.clinicaltrials.gov (NCT #02758405); registered 2 May, 2016.*

Résumé

Objectif *Les formulations médicamenteuses péridurales et les paramètres optimaux pour une analgésie du travail obstétrical en mode PIEB (bolus péridural intermittent*

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programmé) n'ont pas encore été déterminés. Dans une étude précédente, nous avons démontré que des bolus de 10 mL de bupivacaïne 0,0625 % avec 2 μg·mL^{-1} de fentanyl, administrés toutes les 40 min, procuraient à 90 % des femmes une analgésie efficace et sans incidence de percées de douleur paroxystique pendant le premier stade du travail. Dans cette étude, nous avons souhaité déterminer l'intervalle efficace entre les bolus de 5 mL de bupivacaïne 0,125 % avec 2 μg·mL^{-1} de fentanyl administrés en mode PIEB en respectant les mêmes conditions d'étude, ayant à l'esprit la réalisation d'une future étude comparative.

Méthode *Cette étude de détermination de dose en double insu s'est appuyée sur une méthode d'attribution séquentielle par intervalles croissants et décroissants avec tirage biaisé afin de déterminer l'intervalle de PIEB efficace à 90 % (IE90) nécessaire pour procurer une analgésie efficace sans incidence de percées de douleur paroxystique pendant le premier stade du travail obstétrical. Nous avons utilisé des bolus fixes de 5 mL de bupivacaïne 0,125 % avec 2 μg·mL^{-1} de fentanyl et étudié des intervalles de 60, 50, 40 et 30 min. Un intervalle de 60 min a été attribué à la première patiente et les intervalles subséquents ont été attribués selon une méthode de tirage biaisé par suites croissantes et décroissantes.*

Résultats *L'IE90 estimé était de 36,5 min (intervalle de confiance [IC] 95 %, 34,0 à 39,0) selon la méthode Dixon et Mood tronquée et 34,2 min (IC 95 %, 30,8 à 41,5) selon la méthode de régression isotonique. Selon nos observations, 20/40 femmes ont présenté un bloc sensoriel à la glace supérieur à T6, 34/40 femmes n'ont eu aucun bloc moteur, et aucune femme n'a dû être traitée pour de l'hypotension.*

Conclusion *L'IE90 entre les bolus de 5 mL de bupivacaïne 0,125 % avec 2 μg·mL^{-1} de fentanyl pendant le premier stade de travail obstétrical est d'environ 35 min.*

Enregistrement de l'étude *www.clinicaltrials.gov (NCT #02758405); enregistrée le 2 mai 2016.*

The concept of labour analgesia with programmed intermittent epidural boluses (PIEB) has gained much attention in recent years because of the development and availability of drug delivery systems that allow the administration of programmed intermittent boluses coexisting with on-demand boluses, which have been the foundation of patient-controlled epidural analgesia regimens (PCEA). A growing body of evidence based on studies using PIEB for labour analgesia has shown similar or superior quality and longer duration of analgesia compared with continuous epidural infusions (CEI),[1-3] together with higher maternal satisfaction,[4,5] reduced local anesthetic consumption,[2-4,6,7] reduced need for manual rescue boluses,[2-6,8,9] lower incidence of motor block,[6,8] less breakthrough pain,[6] and fewer unilateral blocks.[9]

Most PIEB studies have utilized dilute local anesthetic mixtures of bupivacaine or ropivacaine with fentanyl or sufentanil because evidence suggests that a higher concentration of local anesthetic is associated with more frequent motor block and increased rates of instrumental deliveries.[10] Nevertheless, a more recent meta-analysis[11] looking at the effects of low concentrations and high concentrations of local anesthetic on obstetric and anesthetic outcomes suggests that these conclusions should be interpreted with caution, given the many confounders that may influence those outcomes. Furthermore, most of these studies used CEI, and their results may not be applicable to the PIEB technique.

Different anesthetic solutions and delivery settings have been proposed, and the ideal regimen for PIEB is yet to be determined. Our group has invested in providing analgesia regimens that provide minimum breakthrough pain and minimal usage of PCEA. As such, our group has recently demonstrated that 10 mL boluses of bupivacaine 0.0625% with fentanyl 2 μg·mL^{-1} delivered every 40 min produced effective analgesia without breakthrough pain in 90% of women during the first stage of labour.[12] Nevertheless, 44% of women in this study experienced upper sensory block to ice above the T6 level although this was not associated with motor block or hypotension. We subsequently conducted another study with the same anesthetic solution and the same PIEB interval of 40 min to determine the effective volume (dose) of local anesthetic needed to produce the same outcome of effective analgesia without breakthrough pain.[13] We concluded that the volume (dose) could not be reduced without compromising efficacy, and that, not surprisingly, the sensory block distribution was very similar to that in our first study.[12] The results of the two studies suggest that our regimen provides the minimum hourly amount of local anesthetic required for effective analgesia without breakthrough pain in 90% of women during the first stage of labour.

We believe that the sensory block above the T10 level obtained in both studies, although not determining adverse effects, suggests an imperfect use of the technique with an exaggerated and unnecessary spread of the epidural mixture. It is possible that by limiting the spread of the local anesthetic mixture, we can provide analgesia with less anesthetic. With that in mind, we envisioned using the same dose of bupivacaine but with double the concentration and half of the volume, while maintaining the same concentration of fentanyl. The PIEB regimen using bupivacaine 0.125% with fentanyl 2 μg·mL^{-1} to

produce effective analgesia without breakthrough pain during the first stage of labour has not been investigated. We therefore designed the current study to investigate the optimum time interval between 5 mL boluses of bupivacaine 0.125% with fentanyl 2 $\mu g \cdot mL^{-1}$ needed to produce effective analgesia without breakthrough pain in 90% of women (EI90).

Methods

Following approval by the local research ethics board on April 22 2016, we conducted a prospective double-blind dose-finding sequential allocation trial with the biased coin up-and-down technique. Patients were enrolled from May 2016 to February 2017 at Mount Sinai Hospital, in Toronto, ON, Canada. We obtained written informed consent for the study as soon as feasible after women arrived on the labour unit. When conducting and reporting our investigation, we followed the Consolidated Standards of Reporting Trials (CONSORT) statement.

Inclusion criteria were primiparous women with singleton pregnancy; gestational age $\geq$ 37 weeks; American Society of Anesthesiologists class II or III; induced or spontaneous labour; cervical dilatation between 2 and 5 cm; regular contractions occurring at least every five minutes; and worst contraction pain $>$ 5 on a verbal numerical pain scale (VNPS) 0-10 at the time of request for epidural analgesia. Exclusion criteria were any contraindication to epidural analgesia; unintentional dural puncture; allergy or hypersensitivity to bupivacaine or fentanyl; or consumption of opioids or sedatives within four hours preceding epidural insertion.

All epidural catheter insertions were performed by either a consultant or a fellow with the patient in sitting position at the L3-L4 interspace using ultrasound assistance to ensure consistency of the interspace. Local infiltration was performed using 3 mL of lidocaine 2%. The epidural space was identified by loss of resistance to either air or saline with a 17G Tuohy needle. A 19G multiport wire-reinforced epidural catheter (Arrow FlexTip plus; Arrow International Inc., Reading, PA, USA) was inserted 5 cm into the epidural space. A test dose of 3 mL bupivacaine 0.125% with fentanyl 3.3 $\mu g \cdot mL^{-1}$ was administered. After three minutes, a loading dose was administered consisting of two 6 mL boluses of bupivacaine 0.125% with fentanyl 3.3 $\mu g \cdot mL^{-1}$, given three minutes apart. To continue with the study, we required that a VNPS $\leq$ 1 was achieved within 20 min of administering the loading dose.

In all participants, the epidural infusion pump (CADD-Solis Ambulatory Infusion System, Smith Medical, St. Paul, MN, USA) was set to deliver 5 mL boluses of bupivacaine 0.125% with fentanyl 2 $\mu g \cdot mL^{-1}$ at a delivery rate of 250 $mL \cdot hr^{-1}$, with the first bolus delivered 60 min after the loading dose was administered. Subsequent boluses were delivered at a time interval that was determined by the response of the previous participant to the PIEB regimen, as per the biased coin method. The studied time intervals were 60, 50, 40, and 30 min (groups 60, 50, 40, and 30, respectively); thus, the total hourly bupivacaine volume given by PIEB ranged from 5 mL in group 60 to 10 mL in group 30, corresponding to 6.25-12.5 mg of bupivacaine, respectively. The first PIEB interval time was set at 60 min. The system was also programmed with a PCEA modality to administer 5 mL of the same local anesthetic solution with a lockout interval of ten minutes and a maximum total volume of 15 $mL \cdot hr^{-1}$, including the PIEB and the PCEA. The patient was instructed to press the PCEA button if contractions were uncomfortable. If the patient pressed the PCEA button or requested a physician-delivered top-up, the PIEB regimen was considered inadequate for that specific time interval. If a PIEB time interval did not provide adequate analgesia, the time interval would be lowered by ten minutes for the next patient. On the other hand, if the PIEB time interval provided adequate analgesia, the time interval would either increase with a probability of 1/9, or remain the same. In case of adequate analgesia in group 60 or inadequate analgesia in group 30, the time interval for subsequent patients would remain the same until the biased coin method indicated that the interval time be decreased or increased, respectively. The biased coin up-and-down sequential allocation was carried out using a computer-generated list of random responses prepared by our statistician (X.Y.Y.) using Excel (Microsoft, Redmond, WA, USA). A research assistant used this list to provide the PIEB volume setting for the next woman in a sealed envelope. An unblinded research assistant or consultant anesthesiologist would set up the epidural infusion pump. The epidural infusion pump was covered to ensure the researchers, nurses, and patients remained blinded.

The primary outcome was adequate labour analgesia, which was defined as no use of PCEA or request for manual boluses for six hours after the epidural loading dose was administered or until the woman's cervix was fully dilated, whichever occurred first. We decided for the study duration of six hours since we planned to exclusively study the effectiveness of this PIEB regimen during the first stage of labour. Secondary outcomes included upper sensory block level to ice, motor block in the lower limbs, and hypotension. Baseline data on each woman included physical characteristics, blood pressure between uterine contractions, type of labour (spontaneous or induced) and use of oxytocin. Patient assessments were then completed by a blinded investigator at 20 and 60 min after the loading dose and then hourly thereafter until the end of the study. Assessments included upper sensory block levels to ice in

the midclavicular line, pain scores (VNPS 0-10), non-invasive blood pressure measurements between contractions and degree of motor blockade (modified Bromage score: 0 = no motor block; 1 = inability to raise extended leg but able to move knees and feet; 2 = inability to raise extended leg and move knee but able to move feet; 3 = complete motor block of limb).

For statistical analyses and sample size justification for a dose-finding study using the biased coin up-and-down design, the distribution of data is unknown and non-independent, and therefore prevents the development of theoretical rules to estimate the sample size based on a pre-specified precision of the EI90. Nevertheless, simulation studies suggest that the stopping rule of enrolling at least 20 to 40 patients will provide stable estimates of EI90 for most realistic scenarios.[14-16] Therefore, similar to previous studies, a sample size based on the stopping rule of 40 women was chosen for this study.

The EI90, defined as the analgesia dosing time interval at which the probability of the primary outcome of success was 90% in the study population, was estimated via two methods: the truncated Dixon and Mood (DM) method[15,16] and the isotonic regression method.[15,16] To specify[15,16] let $\Omega = \{x(1) < x(2) < \cdots < x(k)\}$ be the k dosing time interval investigated and $p(i)$ be the observed rate of the primary outcome of success at dose $x(i)$, $i = 1, 2, 3, \ldots, k$. Under the biased coin up-and-down design targeting EI90, the allocated dosing time interval cluster unimodally around the EI90. As a nonparametric estimator of EI90, the DM estimator is the truncated simple mean of the dosing time interval assigned, for example, $\hat{U} = \frac{1}{n-s+1}\sum_{j=s}^{n} x(j)$, where $x(j)$ is the dosing time interval administered to the$j$th woman, s=max{j: the first j patients having the same response}. The isotonic regression estimator of EI90 is the linear interpolated dose between the $p*(r)$ and $p*(r+1)$: $\hat{U}3 = \frac{0.9-p*(r)}{p*(r+1)-p*(r)}(x(r+1)-x(r))+x(r)$, where $x(r) = \max(x(i): p*(i) \le 0.9)$ and $p*(i)$ the adjusted rate of the primary outcome of success at dosing time interval $x(i)$, $i = 1, 2, 3, \ldots, k$, estimated by the pooled-adjacent-violators algorithm (PAVA).[16] Since the observed rate of $p = \{p(1), p(2), \ldots, p(k)\}$ may not be increased with respect to the dosing time interval level, which is the implicit assumption of the dose-finding study, the PAVA algorithm was first used in isotonic regression to obtain an increase adjusted rate $p* = \{p*(1) \le p*(2) \le, \ldots, \le p*(k)\}$ based on p. The 95% confidence interval (CI) of isotonic regression estimator of EI90 was obtained by a bias-corrected percentile method[17] using 2,000 bootstrap replications of $\hat{U}3$. Each replication was obtained by drawing a bootstrap data set with a sample size of 40 and a biased coin up-and-down design, assuming the true dose-response rate at each dosing time interval is $p*(i)$, $i = 1, 2, 3, \ldots, k$estimated based on the original data, and then estimated $\hat{U}3$, the isotonic regression estimator of EI90 based on the bootstrap data.

The DM estimator is more intuitive and simple. If the observed response rates for all administered dosing time intervals are less than the target percentile, i.e., 90%, DM methods may provide more information if the true targeted dosing time interval falls within the time interval sequence investigated,[16] as per the hypothesis. Nevertheless, generally speaking, the estimate based on the isotonic regression method has less bias and lower mean square error[16] than the DM estimator, although a wider confidence interval is expected, and therefore it was recommended to be used as the primary result.

The study population and secondary outcomes were summarized with descriptive statistical methods. Statistical analyses were performed using SAS 9.3 (SAS Institute Inc; Cary, NC, USA) and R package (R version 3.1.3; www.r-project.org).[15]

Results

Seventy-seven eligible women were approached to participate in the study from May 2016 to March 2017. Twenty women declined to participate, and ten women were ineligible to participate. Of the 47 women that consented to participate, three were ineligible following administration of the loading dose (one delivered before the first PIEB, one went for Cesarean delivery, and one had a pain score greater than 1/10 at 20 min after receiving the loading dose). A further three women were excluded as they pressed their PCEA buttons within ten minutes of the first PIEB. One patient withdrew three hours into the observation period because a motor block developed on one side (Bromage score 1). Hence, 40 subjects were included in the data analysis.

Patient demographics and labour characteristics are shown in Table 1. The patient allocation sequence and response to different PIEB interval times are shown in the Figure. The response rate for each time interval group, along with the adjusted response rates, and the time to first bolus rescue in participants who failed to reach adequate anesthesia are presented in Tables 2 and 3. The estimated EI90 with the truncated DM method was 36.5 min (95% CI, 34.0 to 39.0), whereas the estimated EI90 by the isotonic regression method was 34.2 min (95% CI, 30.8 to 41.5). The precision of the estimate was adequate for the different methods as our primary hypothesis was that PIEB interval would range from 30 to 60 min. Women in the 30 min and 40 min groups had adequate analgesia at a rate of 95% and 83%, respectively

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

Age (yr)	32.5 (4.6)
Gestational age (weeks)	39.4 (1.3)
Weight (kg)	81.3 (19.0)
Height (cm)	165.7 (9.4)
BMI ($kg \cdot m^{-2}$)	29.6 (6.5)
Labour (*n* (%)	
Spontaneous	26 (65.0)
Induced	14 (35.0)
Oxytocin administration, *n* (%)	13 (32.5)
Cervical dilation at onset of study, median [IQR]	3 [3-4]
Cervical dilation at study completion, median [IQR]	8 [5.5-10]

Values are mean (SD), number (%), or median [IQR]

BMI = body mass index; IQR = interquartile range; SD = standard deviation

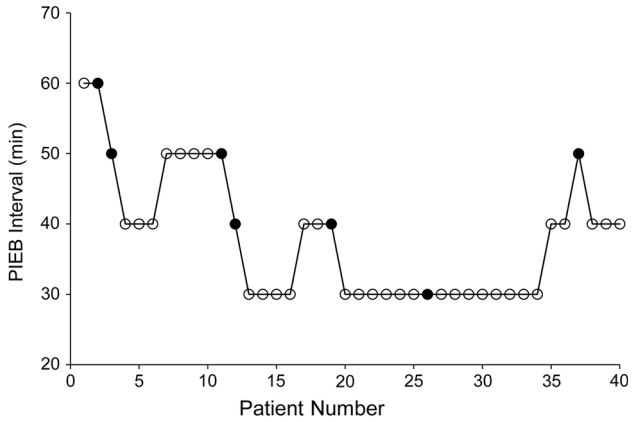

Figure Individual responses of study participants to different programmed intermittent epidural bolus (PIEB) time intervals. Solid circle = adequate PIEB time interval; open circle = inadequate PIEB time interval

Table 2 Observed and PAVA-adjusted rates

PIEB interval (min)	Adequate analgesia	Number of patients	Observed response rate (%)	PAVA-adjusted response rate (%)
60	1	2	50	50
50	4	7	57	57
40	10	12	83	83
30	18	19	95	95

PAVA-adjusted response rates were estimated using a weighted isotonic regression method

PAVA = pool-adjacent-violators algorithm; PIEB = programmed intermittent epidural bolus

Table 3 Timing of patient-controlled epidural analgesia administration for each instance of inadequate analgesia with the proposed PIEB regimen

Patient	PIEB interval (min)	Time to failure (min)
1	60	136
2	50	160
3	50	190
4	40	149
5	40	295
6	30	170
7	50	153

PIEB = programmed intermittent epidural bolus

Regarding upper sensory block levels to ice, all subjects reached a block equal or above that required for labour analgesia. Nevertheless, 52.6% and 58.3% of women had a sensory block level to ice above T6 in the 30- and 40-min groups, respectively. No participants experienced motor block in the 40, 50, or 60-min groups. Four participants (21.1%) in the 30-min group developed a modified Bromage score of 1 and two participants (10.5%) a score of 2. Hypotension occurred in the 30, 40, and 50-min groups, but no participants were symptomatic or required pharmacologic treatment with vasopressors. Table 4 presents the incidence of upper sensory levels, motor block, and hypotension for each group.

Discussion

Our study demonstrates that the optimum PIEB interval time to provide effective analgesia in 90% of women during first stage of labour with 5 mL boluses of bupivacaine 0.125% with fentanyl 2 $\mu g \cdot mL^{-1}$ is approximately 35 min. The calculated amount of local anesthetic delivered was 10.7 $mg \cdot hr^{-1}$, which is in keeping with the findings of several studies done with different concentrations of local anesthetic.[3,7,12] The incidence of motor block and hypotension was very low and similar to our previous two studies using bupivacaine 0.0625%.[12,13] It can also be noted that, despite the low overall incidence of motor block, at 30 min interval approximately 31% of the patients presented some degree of motor impairment.

One of the motivations behind the current study was to optimize the local spread of anesthetic mixture. We wanted to determine the EI90 of bupivacaine 0.125% with the aim of conducting a comparative trial with our current regimen of bupivacaine 0.0625%. One of the reasons we wanted to pursue smaller volumes of a more concentrated solution was that our current technique is associated with a wide

Table 4 Sensory block levels to ice, and hypotension and motor block in women receiving programmed intermittent epidural bolus analgesia

	Interval (min)			
	30 (n = 19)	40 (n = 12)	50 (n = 7)	60 (n = 2)
Highest sensory block level to ice over study period (n, %)				
T2	2 (10.5)	2 (16.7)	1 (14.3)	0 (0.0)
T3	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)
T4	5 (26.3)	2 (16.7)	1 (14.3)	0 (0.0)
T5	3 (15.8)	2 (16.7)	1 (14.3)	0 (0.0)
T6	5 (26.3)	2 (16.7)	2 (28.6)	1 (50.0)
T7	2 (10.5)	1 (8.3)	1 (14.3)	0 (0.0)
T8	2 (10.5)	1 (8.3)	1 (14.3)	0 (0.0)
T9	0 (0.0)	1 (8.3)	0 (0.0)	1 (50.0)
Degree of motor block (n, %)				
Bromage score				
0	13 (68.4)	12 (100.0)	7 (100.0)	2 (100.0)
1	4 (21.1)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypotension (n, %)	1 (5.3)	2 (16.7)	2 (28.6)	0 (0.0)
Patients requiring treatment (n, %)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Sensory block and degree of motor block refer to the highest/densest level of the block over the entire study period. The definition of hypotension was a drop in blood pressure of greater than 20% from baseline at any point during the study

spread of the sensory block. It was our hypothesis that reducing the volume while keeping the dose would avoid unnecessary excessive spread. Interestingly, the distribution of the upper sensory levels to ice in this study seems very similar to what we obtained in our previous studies while using the same dose of bupivacaine but in a volume two times larger.[12,13] Although PIEB regimens are overall more effective than CEI regimens, higher volumes of dilute local anesthetic solution, while associated with less motor block,[8,9] may reach higher sensory block levels to ice than those required for analgesia during labour. In our institution, sensory blocks to ice above the T6 level generate a warning concern for nurses and consequently increase the workload for the anesthesia team.

This wider sensory block is because bolus delivery, when compared with continuous infusion, results in greater longitudinal extent of circumferential spread in both cephalic and caudad directions.[17,18] It is possible that these higher sensory blocks are unavoidable when adequate analgesia is achieved with PIEB and may warrant a change to the nursing protocols at our institution. It is important to emphasize that these high sensory blocks did not result in any significant hypotension.

Our study has some limitations. Our results may not be applicable to nulliparous women beyond 5 cm of cervical dilatation or multiparous women. Our study follow-up was set to terminate at six hours, and it may not be applicable to women who undergo a longer first stage of labour. Finally, our PIEB regimen may not be effective for women in the second stage of labour since the additional somatic component may require a higher dose of local anesthetics.[19]

In conclusion, the EI90 between 5 mL boluses of bupivacaine 0.125% with fentanyl 2 $\mu g \cdot mL^{-1}$ under the studied conditions is approximately 35 min. This information is important for clinicians willing to use bupivacaine 0.125% as the maintenance solution for their PIEB technique. This information is also important for future comparative studies with boluses of the same dose of bupivacaine 0.0625%, as it relates to the performance of the PIEB technique during the first and possibility second stage of labour.

Competing interests None declared.

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