



Patient intermittent epidural boluses (PIEB) plus very low continuous epidural infusion (CEI) versus patient-controlled epidural analgesia (PCEA) plus continuous epidural infusion (CEI) in primiparous labour: a randomized trial

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Abstract

Epidural maintenance technique for labour analgesia updates constantly. Thanks to infusion pumps, the recently developed programmed intermittent epidural bolus (PIEB) may reduce the use of anesthetic drugs and minimize unintended consequences such as cardio or neurotoxicity. Nevertheless, it is not yet a general practice. So far, there are no comparative studies in the literature that address levobupivacaine-based CEI + PCEA versus CEI + PIEB + PCEA. A randomized double-blind trial was carried out to evaluate if PIEB could reduce local anesthetic use compare to PCEA. Primiparous pregnant patients were divided into two groups: PIEB group (continuous infusion plus intermittent automatic doses) and PCEA group (continuous infusion plus PCEA). The primary objective was to analyze the differences between both groups regarding levobupivacaine total dose. The secondary objectives were to find out the differences concerning pain control, motor blockage, satisfaction score, labour time and delivery outcomes. Statistical analyses were done by protocol. The study recruited 200 patients (103 PIEB, 97 PCEA). The total dose administered was significantly higher in PIEB group: PCEA group 52.97 mg, IC 95% 45.65–60.28 mg and PIEB group 62.04 mg, IC 95% 55.46–68.61 mg ($p=0.021$). PIEB group required fewer top up boluses (median value 1; range 0–2) than CEI + PCEA group (median value 6; range 3–9) $p < 0.05$. Satisfaction scores were higher in PIEB group ($p=0.039$, CI 95% 1.23–1.42). CEI + PIEB was found to be a good alternative to CEI + PCEA with very high rates of satisfaction in both groups although it was higher in PIEB group. PIEB group required fewer PCEA boluses. Further studies are needed to determine the best approach for epidural pain management.

Clinical Trial Number and Registry URL: NCT03133091 (<https://clinicaltrials.gov/ct2/show/NCT03133091?term=MB+Rodríguez&rank=1>).

Keywords Patient-intermittent epidural boluses · Patient-controlled epidural analgesia · Obstetric epidural analgesia · Levobupivacaine

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1 Introduction

Epidural analgesia during labour is one of the most demanded techniques by anesthetists. It provides the best analgesia and facilitates maternofetal wellbeing with good outcomes [1].

With the development of epidural infusion pumps, maintenance techniques for labour analgesia have evolved in the past decades. The first technique was intermittent manual boluses injections (IB, intermittent boluses). After that, continuous infusions with or without patient demand appeared, namely, continuous epidural infusion (CEI) or patient-controlled epidural analgesia (PCEA) [2]. The recently

developed programmed intermittent epidural bolus approach (PIEB) consists of intermittent programmed boluses without patient control. The latest pumps on the market also offer the possibility to make use of both modes (PIEB and PCEA) [2, 3]. When compared to CEI, Wong et al. point out that PIEB may reduce anesthetic use and minimize unintended consequences such as undesirable motor block or toxicity effects [3]. PIEB automatic boluses combine advantages offered by CEI and manual boluses such as the absence of fluctuations in sensory levels and less need for PCEA administration [3]. Neither time rate nor PIEB lockout period has been defined as the best option. Nevertheless, it has been reported that by increasing boluses volume and time intervals, local anesthetic use may decrease, obtaining the same degree of satisfaction as in CEI + PCEA [3–5]. PIEB limits the disadvantages of both CEI and manual boluses. CEI is associated with greater local anesthetic consumption, which may increase maternal motor blockage [6] and, as a result, more dystocic and instrumental deliveries may appear. PIEB studies show more satisfaction [3, 7–11] compared to other maintenance techniques. PIEB use is extending in the US, where more maternal satisfaction has been observed [3]. However, it is not yet common practice.

Despite its widespread use, not only in obstetrics anesthesia but also in regional blocks [3], there are few studies on levobupivacaine-based epidural analgesia [8], as most of them have been performed using bupivacaine or ropivacaine [7–11]. Levobupivacaine may reduce motor blockade as much as ropivacaine does, in contrast with bupivacaine, and levobupivacaine analgesic effect lasts longer than ropivacaine [12]. With equipotent doses, ropivacaine may need more boluses than levobupivacaine [13, 14]. Lower concentrations of local anesthetic are related to lower rate of instrumental vaginal delivery [15]. Thus, our hypothesis is that CEI + PIEB maintenance technique with low levobupivacaine concentration (0.0625%) + fentanyl in primiparous females may reduce total levobupivacaine dose, motor block and, consequently, the need for instrumental delivery.

A randomized trial was conducted to evaluate if PIEB could reduce local anesthetic drugs and obtain the same level of satisfaction as PCEA maintenance technique. The primary objective was to find out whether there were significant differences in both groups regarding levobupivacaine total dose.

2 Materials and methods

A double-blind randomized trial with a pharmacological approach and equivalence analysis including the different objectives was carried out. This study was approved by the Spanish Agency for Medicinal Products and Medical

Devices (AEMPS) and was conducted in the Rio Hortega University Hospital (HURH).

After obtaining Institutional Ethics Committee approval and written informed consent, healthy primiparous term females with vertex presentations were selected to participate in the study. The randomization was made with a random number table to produce sequentially opaque numbered envelopes containing the assigned group. The sample size was calculated with a previous pivotal trial in order to avoid an error type I of 0.05 and ensure a statistical power of 0.99. Therefore, the sample size result was 190 patients to be randomized. An estimated 10% loss was added and 210 envelopes were made out.

The mean sample difference divided by the whole sample standard deviation of the primary objective was assumed to be 0.5. The results will be expressed as mean \pm standard deviation. The statistical analysis was done with SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The 99% statistical power and the 95% standard deviation were calculated from the beginning.

The Good Clinical Practice Guidelines and the revised recommendations of the CONSORT [16] statement for manuscript presentation were followed. Patients were recruited between September 2015 and July 2017.

The primary objective was to evaluate the differences in total dose of levobupivacaine administered in both groups (PIEB and CEI + PCEA). The difference was calculated obtaining the total dose from the infusion pump. PCEA boluses were added to total consumption.

Secondary goals and assessment tests (Supplementary Digital Content 1) were:

- Pain control: pain evaluation was done with Visual Analog Scale (VAS) [17, 18]. Pain control was assessed before epidural puncture, 15 min after the puncture and 3 h thereof. Patients continued in the study if their pain was lower than 10 after 15 min of epidural puncture.
- Differences in satisfaction degree (Likert Scale): 1 = very satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = not satisfied and 5 = not satisfied at all. This is a validated scale that not only measures satisfaction, but also, points out the degree of fulfillment of the proposed question posed one hour after labour.
- Delivery: vaginal, instrumental or caesarian section.

2.1 Inclusion/exclusion criteria

Inclusion criteria comprise primiparous females, pregnancy to term, aged between 20 and 40 with no pregnancy-risk illnesses, no drug allergies and a normal initial onset of epidural block. Hereafter, the patients had to understand the procedure and sign the informed consent. They had the right to leave the trial whenever they wished. The study was

carried out with all the primiparous patients who requested epidural analgesia when they experimented 3–7 cm of cervical dilation and met the inclusion criteria. No intrapartum opioids were collected, as their administration is unusual in our hospital.

Patients excluded from the study were those whose illnesses involved pregnancy risk or epidural contraindications, levobupivacaine allergy, multiparous females, epidural catheter replacement due to an initial incomplete onset of the block or those who failed to understand the procedure or refused to sign the informed consent.

2.2 Technique/protocol

At the time of analgesia demand during labour, cervical dilation was between 3 and 7 cm and epidural analgesia was administered. Baseline pain was evaluated with VAS scale. Epidural puncture was placed at L2–L3 or L3–L4 with the patient seated. The epidural space was identified by loss-of-resistance to air (1–2 ml). After verifying no free cerebrospinal fluid was present, the multi-orifice epidural catheter (3–4 cm) was placed. A 10 ml levobupivacaine 0.125% bolus was administered together with 2 mcg/ml fentanyl. The catheter was attached and a nurse—not participating in the delivery—set up the epidural pump (Smiths CADD SOLIS™), following the information in the randomized envelopes, which were opened after epidural puncture. Neither the patient nor the anaesthetist was aware of this setting. Levobupivacaine 0.0625% + fentanyl 1 mcg/ml was administered through a particle filter into a polyamide catheter. The patients were divided into two groups: PIEB group with a 2 ml/h continuous infusion plus a 7 ml/30 min PIEB bolus. If the PIEB group patients required PCEA (6 ml/20 min), then the next PIEB bolus was delayed. The second group (CEI + PCEA) had a continuous infusion of 5 ml/hour plus 6 ml/20 min PCEA. This calculation was made in order that both groups received theoretically the same dose per hour, provided that PCEA group patients requested all possible boluses in an hour. The patients were shown how and when to press the button of the PCEA pump.

The total anesthetic dose was registered by the epidural pumps and gathered after child and placenta delivery. PCEA records were also based on the epidural pumps.

2.3 Statistical analysis

Descriptive and inferential statistical analysis of the satisfaction data was performed by protocol.

The Kolmogorov–Smirnov test was used to establish the normality of the quantitative variables. Normal distribution variables were described as the mean \pm standard deviation (SD) and those of non-normal distribution and/or discrete distribution were taken as the median and interquartile

range. Furthermore, the qualitative variables are presented in a table of absolute and relative frequencies (percentages) of their categories. Finally, error bars (normal variables) or box diagrams (non-normal variables) represent the quantitative variables. Bar graphs (with 95% CI) show the qualitative variables.

In order to study the relationship between qualitative variables, χ^2 test with Fisher's exact test (tables 2×2) or likelihood ratio (more than 2 categories) were used, according to their application conditions (expected frequency < 5 in more than 20% of the boxes).

Student T-test or Mann–Whitney U test were employed to study the differences between independent means, according to the application conditions (normality) for 2 groups.

Student T-test for related samples was carried out to study the differences between related means (baseline versus evolution/outcome). A p level < 0.05 was considered as statistically significant. SPSS version 15.0 (SPSS INC., Chicago, IL, USA) was used to process data.

3 Results

Data was collected over a period of 22 months and 200 patients were randomized, 103 in CEI + PIEB group and 97 in CEI + PCEA group. Five patients who needed a new epidural puncture were excluded (3 from CEI + PIEB group and 2 from CEI + PCEA group); 2 due to lateralization and 3 for ineffective pain assessment (Fig. 1, Flowchart). Both groups reached the statistical power required.

The total levobupivacaine dose was statistically significant higher in PIEB group. PIEB received 62.04 mg (CI 55.46–68.61 mg) and CEI + PCEA group 52.97 mg (CI 45.65–60.28) ($p = 0.021$), with an estimated 99% statistical power (Fig. 2). PIEB group received fewer PCEA boluses (median value 1; range 0–2) than CEI + PCEA group (median value 6; range 3–9) $p < 0.05$. (Supplementary Digital Content 2).

Pain control in all stages was similar (Supplementary Digital Content 3) in both groups. Analgesia management valued through subject satisfaction was well scored in both groups. 74.7% confirmed they were “very satisfied” (Likert 1) and there were only 9 cases whose satisfaction was > 3 (not very satisfied), dissatisfaction was not statistically different among groups 8/97 PCEA group versus 3/103 PIEB group ($p = 0.26$). CEI + PCEA obtained lower satisfaction mean 1.48 (CI 1.31–1.64) compared to PIEB 1.21 (CI 1.12–1.31). Additionally, more patients from PIEB group defined their satisfaction as “very satisfied” (Likert 1). Statistical significance was found ($p = 0.039$), although it was not clinically relevant (Fig. 3).

There were no significant differences neither regarding type of delivery, nor vaginal tears or episiotomy in either

Fig. 1 Flowchart

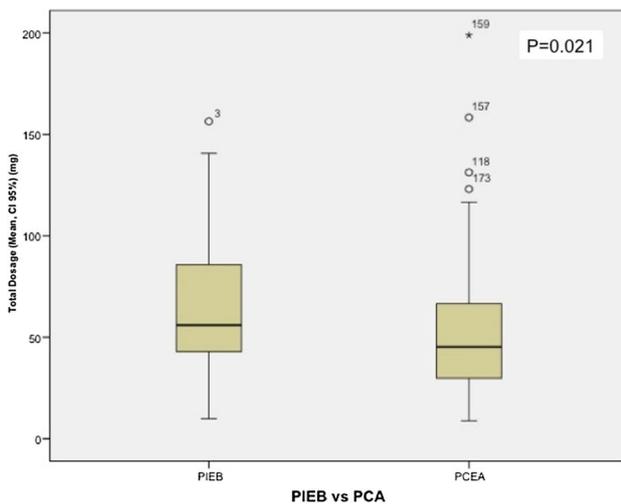
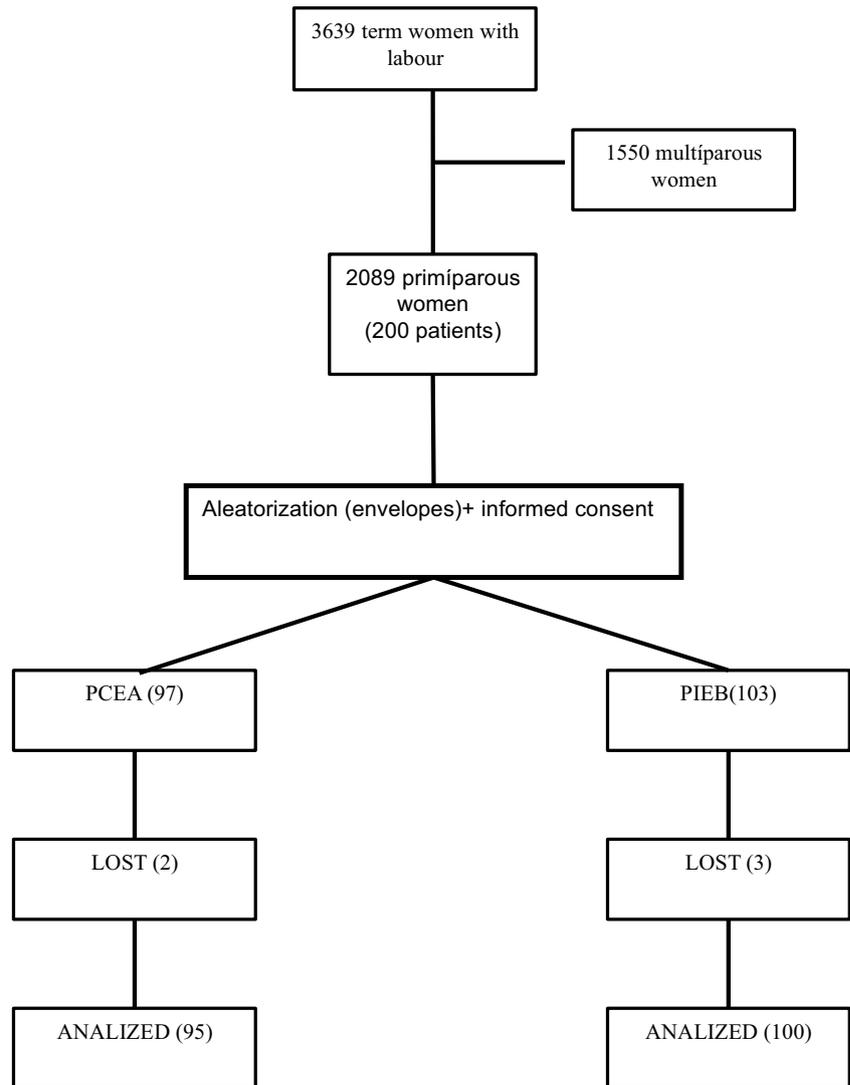


Fig. 2 Total levobupivacaine dose

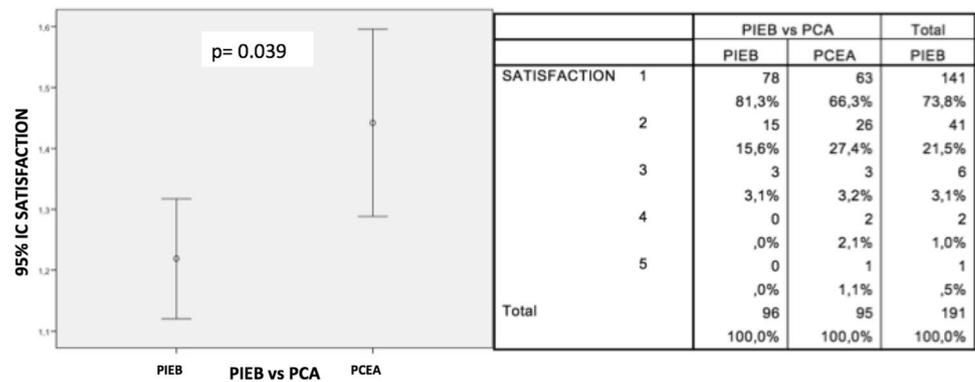
group, but instrumental deliveries were more frequent in the PIEB group (21.4% PIEB versus 11.6% CEI+PCEA). (Supplementary Digital Content 4).

4 Discussion

Our results showed that CEI+PIEB patients did not receive a lower dose than the CEI+PCEA group. Anesthetic consumption contrasts with the literature reviewed [3, 8, 19, 20] regarding other local anesthetic drugs. Capogna et al. [8] reported 145 patients whose consumption of local anesthetic in the PIEB group (31 mg, CI 25–38 mg) was lower than the CEI group (37 mg, CI 31–44 mg); patients requiring additional PCEA boluses were also lower in the PIEB group (6 vs. 28). Other studies [3, 21] confirmed these results.

The difference observed in our study may be due to the fact that the trial was made on primiparous patients.

Fig. 3 Satisfaction Likert Scale



Therefore, the dilatation period was longer. This may result in receiving more automatic PIEB boluses. Furthermore, the dilation period may determine more PCEA required by the patients [8]. This assumption has also been highlighted in other studies [22]. On the other hand, labour was induced in some of the patients, which is more painful, and may have needed early epidural administration [23].

A major concern might be dosage differences between groups, as the basal dose is higher in the PIEB group, if the patients did not require the maximum allowed PCEA boluses in the CEI + PCEA group. The higher basal dose can also lead to a lower use of PCEA in the PIEB group. There is not a specific gold standard regarding the mode of local anaesthetic administration in PIEB. Neither time rate nor PIEB lockout period has been defined properly as the best option.

Our study uses similar doses and lockout periods (7 ml/30 min PIEB) to other proposals that obtained good results in other studies (5–9 ml/30–45 min PIEB) [3, 24, 25]. Nevertheless, small doses and longer lockout periods have also had good outcomes (5 ml/60 min PIEB) [9, 20, 21, 26]. Recently, Bullingham et al. [27] reported a lower dose of anesthetic with less motor block using PIEB 5 ml/h + PCEA compared with CEI, but anesthetic concentration was different in both groups. However, other studies have shown that by increasing boluses volume and time intervals (10 ml/60 min PIEB), total anaesthetic dose is reduced with similar analgesic effects and patient satisfaction [8, 28, 29]. In another recent study, Delgado et al. reported that there were no differences concerning physician-administered top ups comparing CEI (10 ml/h) + PCEA (5 ml/10 min) with PIEB (10 ml/h) + PCEA (5 ml/10 min), but with longer second labour stage in the PIEB group. However, in the same study, the use of PIEB (10 ml/45 min) + PCEA (5 ml/10 min) showed less demand for physician-administered top ups [30]. To sum-up, the differences in design could clearly affect the results concerning total anesthetic dose.

In addition, the PIEB group needed fewer analgesic boluses and took longer to demand the first bolus. Some authors reported similar results [8, 9, 23, 31].

In our opinion, the most relevant novelty of our study is adding a very low flow of CEI to PIEB. The literature does not gather such a combination so far, but the effects of adding a continuous epidural infusion to PCEA has produced contrasting results. Missant et al. [32] report good analgesia effects, as well as a reduction of local anaesthetic consumption and anaesthetist workload when using PCEA with a very low background infusion (2 ml/h). On the other hand, Brogly et al. [33], in a randomized study using a high volume and long lockout PCEA (10 ml/20 min) protocol, did not find any advantages regarding pain management and maternal satisfaction when adding a high flow background infusion (10 ml/h) to PCEA. In a recent meta-analysis on the benefit of adding background infusion to PCEA, Heesen et al. [11] identified seven trials with a lower risk of bias, however, a definitive conclusion regarding risks or benefits of adding basal continuous infusion to PCEA compared with PCEA alone was not quite achieved. Depending on the specific outcome, adding background infusion to PCEA might be superior or inferior to PCEA alone in epidural labour analgesia.

VAS mean was the same for both groups, as described in several of the studies reviewed [3, 8, 9]. Chua et al. [9] found a significantly lower pain score in the PIEB group than in the CEI + PCEA in the first 3 h of delivery. Sia et al. [34] reported a reduction of hourly consumption of local anesthetic in the PIEB group, which also seems to be a better analgesic option, especially for prolonged deliveries as shown in the literature [26].

Satisfaction was very high in both groups. CEI + PCEA group reported lower statistical significance satisfaction than PIEB group ($p < 0.05$), although the results were not clinically relevant. These results contrast with the ones obtained in other studies [3, 7, 21].

The Likert Scale was used to describe patient satisfaction. It was especially useful as nuance statements were needed, which means the subjects could share and match the order of their statements. Conceptually, the Likert Scale is ordinal, so a drawback may be that parametric statistics tests cannot be

used [35]. However, they can also be used on small sample sizes with unequal variances and non-normal distributions [35].

Despite the higher anesthetic dose in PIEB + CEI group, caesarean sections did not increase, as other studies reported [9, 36]. According to other authors [8, 28], PIEB may be associated with lower risk of caesarean delivery.

Our study presents several limitations. Firstly, the study was designed in such a way that the PIEB group received a higher anesthetic basal dose, compared to the studies reviewed. Secondly, only primiparous females were included in the study in order to make the cohorts as uniform as possible [9]. Thirdly, the dosage was not adapted to the patients' characteristics such as height and body mass. Finally, chronic analgesic intake was not taken into consideration [5].

In conclusion, CEI + PIEB seems to be a good alternative to CEI + PCEA as the need for supplementary PCEA boluses is lower and the satisfaction rates are very high. Although the total dose of levobupivacaine may increase, there are no clinical consequences. Further studies are needed to determine the best approach for epidural pain management.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interests.

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