

# 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

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**BACKGROUND:** Programmed intermittent epidural anesthetic bolus (PIEB) technique may result in reduced total local anesthetic consumption, fewer manual boluses, and greater patient satisfaction compared with continuous epidural infusion (CEI). In this randomized, double-blind study, we compared the incidence of motor block and labor outcome in women who received PIEB or CEI for maintenance of labor analgesia. The primary outcome variable was maternal motor function and the secondary outcome was mode of delivery.

**METHODS:** Nulliparous, term women with spontaneous labor and cervical dilation <4 cm were eligible to participate in the study. Epidural analgesia was initiated and maintained with a solution of levobupivacaine 0.0625% with sufentanil 0.5 µg/mL. After an initial epidural loading dose of 20 mL, patients were randomly assigned to receive PIEB (10 mL every hour beginning 60 minutes after the initial dose) or CEI (10 mL/h, beginning immediately after the initial dose) for the maintenance of analgesia. Patient-controlled epidural analgesia (PCEA) using a second infusion pump with levobupivacaine 0.125% was used to treat breakthrough pain. The degree of motor block was assessed in both lower extremities using the modified Bromage score at regular intervals throughout labor; the end point was any motor block in either limb. We also evaluated PCEA bolus doses and total analgesic solution consumption.

**RESULTS:** We studied 145 subjects (PIEB = 75; CEI = 70). Motor block was reported in 37% in the CEI group and in 2.7% in the PIEB group ( $P < 0.001$ ; odds ratio = 21.2; 95% CI: 4.9–129.3); it occurred earlier ( $P = 0.008$ ) (hazard ratio = 7.8; 95% CI: 1.9–30.8;  $P = 0.003$ ) and was more frequent at full cervical dilation in the CEI group ( $P < 0.001$ ). The incidence of instrumental delivery was 20% for the CEI group and 7% for the PIEB group ( $P = 0.03$ ). Total levobupivacaine consumption, number of patients requiring additional PCEA boluses, and mean number of PCEA boluses per patient were lower in the PIEB group ( $P < 0.001$ ). No differences in pain scores and duration of labor analgesia were observed.

**CONCLUSIONS:** Maintenance of epidural analgesia with PIEB compared with CEI resulted in a lower incidence of maternal motor block and instrumental vaginal delivery. (Anesth Analg 2011; X:●●●—●●●)

Neuraxial analgesic techniques, such as epidural and combined spinal-epidural (CSE) analgesia, are the most effective modalities for pain relief in labor. Once analgesia has been established, either by using an epidural or a CSE technique, the maintenance of analgesia throughout labor until delivery may be obtained with different techniques. With intermittent epidural bolus injection (top-up) of the analgesic solution, frequent provider interventions are required, and the parturient may experience intervals of analgesia after the dose takes effect alternating with intervals of pain as the analgesia wanes. Continuous infusion results in a smoother analgesic experience for the parturient with fewer medical interventions,

but total anesthetic doses are usually larger and motor block may be more profound.<sup>1</sup> There is some evidence from anatomical and in vitro studies<sup>2,3</sup> that uniform diffusion of local anesthetic in the epidural space, which leads to greater efficacy, is better obtained by the administration of bolus rather than continuous infusion.

Automated systems designed to administer a bolus at programmable intervals (programmed intermittent epidural anesthetic bolus [PIEB] technique) to combine the advantages of both manual bolus and continuous infusion, have recently been introduced. Wong et al.<sup>4</sup> compared PIEB versus continuous epidural infusion (CEI) in induced parous women. They reported less total local anesthetic consumption, fewer manual bolus doses because of breakthrough pain, and greater patient satisfaction with the PIEB technique. In their study, they noticed that the beneficial effect of PIEB was significant in women with longer labors, and therefore, they hypothesized that PIEB would be of greater value in parturients with longer labors such as spontaneously laboring nulliparous women.

Other studies have confirmed these findings in nulliparous women.<sup>4–6</sup> Previous studies have used either an epidural or

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CSE technique to initiate neuraxial analgesia. Programmed bolus volumes and time intervals, and anesthetic solutions, vary among studies. However, it has been reported that a large volume administered every 60 minutes compared with smaller volumes administered every 15 to 30 minutes did not increase the extent and density of sensory blockade, but decreased bupivacaine consumption and variability without decreasing patient comfort and satisfaction.<sup>7</sup>

None of the previous PIEB studies aimed to evaluate the effects on maternal motor function. Although motor function and mode of delivery were reported as secondary outcomes, these studies were not adequately powered to address differences in these outcomes. Women who received labor analgesia with higher compared with lower concentrations of local anesthetic have a significantly higher rate of instrumental vaginal delivery<sup>8</sup> and this is generally believed to be related to a decrease in motor function because of the high concentration of local anesthetic. Furthermore, most patients find the inability to move their legs distressing. Many prefer to ambulate during labor, allowing them to get up to use the bathroom. For these reasons, analgesic techniques that minimize motor block are preferred.

The aim of this study was to test the hypothesis that PIEB may decrease the incidence of motor block and instrumental delivery, while maintaining adequate analgesia, compared with CEI. For the purpose of the study, we used a low concentrate solution of levobupivacaine with sufentanil administered at the same volume per hour. The primary outcome was the incidence of maternal motor block throughout labor and the secondary outcome was mode of delivery.

## METHODS

This prospective, randomized, double-blind, controlled study was approved by the Clinical Research and Ethics Committee of Città di Roma Hospital. Healthy, nulliparous, term women with singleton, vertex pregnancies in spontaneous labor were eligible to participate in the study, which was performed at Città di Roma Hospital, Roma. Women with any disorder of pregnancy, breech or multiple gestation, who had received parenteral opioids or required oxytocin before epidural analgesia, or who were unable to perform motor block evaluation tests, were excluded from the study.

At the time of request for labor analgesia, cervical dilation and baseline pain scores were noted. The parturient was admitted to the study if cervical dilation was <4 cm and if her baseline pain score, assessed at the peak of the contraction, was >50 on a 100-mm visual analog pain scale (VAPS) (100-mm unmarked line with end points labeled "no pain" and "worst pain imaginable"). Women who met the above criteria were approached for study participation and were requested to give written informed consent to participate.

Immediately before initiation of analgesia, an IV infusion of 500 mL Ringer lactate solution was started, and baseline maternal heart rate, noninvasive arterial blood pressure, and fetal heart rate tracing were recorded. Epidural analgesia was initiated in the left lateral decubitus position at the L3-4 or L4-5 interspace. The epidural space was identified using the loss of resistance to saline technique (1–2 mL) with a 16-gauge Tuohy epidural needle. A closed-end, multiorifice epidural catheter was inserted 3 to

4 cm into the epidural space through the Tuohy needle and secured. No test dose was administered.

All parturients received an initial epidural loading dose consisting of 0.0625% levobupivacaine 20 mL (Chirocaine; Abbott, Chicago, IL) plus sufentanil 10  $\mu$ g (Fentatienil; Angelini, Rome, Italy). Parturients who did not obtain a VAPS score  $\leq$ 10 mm 30 minutes after the epidural injection or who requested a patient-controlled epidural analgesia (PCEA) bolus within 30 minutes were deemed to have a failed block and were excluded from the study and subsequent statistical analysis.

During epidural catheter placement, a sequentially numbered, opaque envelope containing the group assignment (computer-generated random-number sequence) was opened by an unblinded researcher who set up the 2 epidural pumps according to group allocation. The subjects and other study personnel were blinded to group assignment and all the observations and assessments were performed by a researcher blinded to the mode of drug administration. The infusion pumps were inserted into an opaque, portable bag.

For the purpose of the study, we used 2 pumps (GemStar; Hospira, Lake Forest, IL [approved by the United States Food and Drug Administration for epidural infusion]): one pump administered either PIEB or CEI for the maintenance of analgesia and the other pump administered PCEA to treat breakthrough pain. Parturients were randomized to receive one of the following regimens for the maintenance of analgesia: PIEB + PCEA (group PIEB) or CEI + PCEA (group CEI). The PIEB pump was programmed to deliver 0.0625% levobupivacaine with sufentanil 0.5  $\mu$ g/mL, 10 mL every hour, beginning 60 minutes after the administration of the initial epidural loading dose. The CEI group pump was programmed to deliver levobupivacaine 0.0625% with sufentanil 0.5  $\mu$ g/mL at a rate of 10 mL/h beginning immediately after the loading dose administration.

The PCEA pump was programmed to deliver 5-mL patient-activated boluses of levobupivacaine 0.125% with a lockout interval of 10 minutes, and a per hour maximum volume of 15 mL. Patients were instructed, before or immediately after the epidural catheter placement, on how to use the PCEA pump and to push the button whenever they felt uncomfortable. All PCEA pumps were made available immediately after the loading dose. Both pumps were inserted into a portable bag-type pouch and the infusion tubing of each was connected to the patient's epidural catheter via a 3-way stopcock. The standard GemStar infusion tubing is equipped with an antireflux valve, thus preventing any reflux of local analgesic solution.

If the parturient still felt pain after activating the PCEA bolus twice in a 20-minute period, an anesthesiologist administered additional manual incremental boluses of 5-mL levobupivacaine 0.125% until the VAPS score was <10 mm. The epidural infusions (PIEB or CEI and PCEA) were continued through the second stage of labor until delivery of the fetus.

Data noted for each subject included demographic characteristics, labor data, analgesia and motor block evaluation, and mode of delivery. The records of the epidural infusions including PCEA requests, delivered PCEA boluses, and total

infused volumes were obtained from the infusion pump history. The number and total volume of manual rescue boluses were recorded. Local anesthetic administered specifically for instrumental assisted vaginal delivery analgesia was not included in the total drug calculation.

VAPS score for pain and motor function was evaluated every 60 minutes beginning 30 minutes after the epidural injection during the first stage of labor and at full cervical dilation (before pushing). The degree of motor block was assessed in both lower extremities using the Breen modified Bromage score,<sup>9</sup> whereby 1 = complete block (unable to move feet or knees); 2 = almost complete block (able to move feet only); 3 = partial block (just able to move knees); 4 = detectable weakness of hip flexion while supine (between scores 3 and 5); 5 = no detectable weakness of hip flexion while supine (full flexion of knees); and 6 = able to stand and to perform partial knee bend. The end point was the occurrence of any degree of motor block in one or both lower limbs at any time during labor.

Our primary end point was the incidence of motor block (modified Bromage score <6). Based on results of previous studies,<sup>10</sup> we anticipated that 30% of women would experience motor block during labor using CEI, and that PIEB would lead to an incidence of motor block <10%. A sample size of 70 subjects in each group guaranteed us a power of at least 80% for a 2-sided  $\chi^2$  test of association between maintenance technique and incidence of motor block, with a significance level set to 0.05.

The secondary end point was the incidence of instrumental vaginal delivery. Based on historical data from our institution, we anticipated 27% of women would have instrumental delivery with CEI. We assumed an incidence of instrumental vaginal delivery in the PIEB group of 6% would be clinically significant. Therefore, the planned sample size also guaranteed a power of at least 80% for a  $\chi^2$  test of association between maintenance technique and incidence of instrumental delivery, with significance level set to 0.05. Ten additional subjects were included in the randomization to allow for anticipated exclusion.

Data were expressed as mean  $\pm$  SD or median  $\pm$  interquartile range where appropriate. Association between categorical variables was evaluated using Fisher exact test or the  $\chi^2$  test if the table was not  $2 \times 2$ . Occurrence of motor block at any time during labor was analyzed using logistic regression. Possible predictors were type of delivery, maintenance group (PIEB or CEI), total anesthetic dose, age, weight, or height. Variable selection was performed through a forward strategy. With the same strategy, we analyzed 2 other outcomes: the incidence of one or more PCEA requests, and the incidence of instrumental delivery. Continuous outcomes, e.g., the total anesthetic dose, were compared between groups with the Mann-Whitney *U* test.

Time to delivery data were described by Kaplan-Meier product limit estimator, survival distributions were compared using the log-rank test, and multivariate analysis was performed using the Cox model. When the outcome was motor block, censoring of time-to-event data was informative because these data are censored by delivery. Consequently, we used a competing risk approach. We reported the subdistribution estimates of the cumulative incidence functions and compared them by means of the Gray test.<sup>11</sup>

For multivariate analysis, we fitted the proportional sub-distribution hazards regression model of Fine and Gray.<sup>12</sup> Finally, we analyzed the total number of PCEA boluses during labor. To do so, we used a longitudinal model with informative censoring by delivery. We used joint mixed-effect models (according to Wulfsohn and Tsiatis<sup>13</sup> and Henderson et al.<sup>14</sup>) in which the random effects were subject specific. A shared random effect was used to reduce bias from informative dropout because of the censoring event (delivery).<sup>14</sup> All analyses were performed using the statistical software R 2.9.1 (R Development Core Team, 2009).

## RESULTS

One hundred fifty subjects recruited between April 2009 and July 2010 participated in the study and were randomized to either the PIEB group or the CEI group. Five subjects in the CEI group were lost to follow-up, leaving 145 subjects for the data analysis (PIEB = 75; CEI = 70) (Fig. 1). Subject and labor characteristics are reported in Table 1. Patients in the PIEB group were slightly older than patients in the CEI group.

Motor block occurred at least once during labor in 37% of cases in the CEI group and in 2.7% of cases in the PIEB group ( $P < 0.001$ ). The odds ratio for the occurrence of motor block was 21.2 (95% CI: 4.9–129.3). Motor block occurred earlier in patients who received CEI with a mean (SD) of 7.8 (2.4) hours versus 9.8 (0.3) hours in the PIEB group ( $P = 0.008$ ) (Fig. 2), and a hazard ratio of 7.8 (95% CI: 1.9–30.8;  $P = 0.003$ ). Motor block was also more frequent at full cervical dilation in patients in the CEI group (25 of 55) compared with the PIEB group (5 of 61) ( $P < 0.001$ ).

Instrumental delivery was performed using the Mityvac vacuum assisted delivery system (Cooper Surgical, Trumbull, CT) in all cases. The incidence of instrumental delivery was 20% for the CEI group and 7% for the PIEB group ( $P = 0.03$ ), with a relative risk of 2.9 (95% CI: 1.1–7.9). The occurrence of motor block at full cervical dilation was associated with an increased risk of instrumental delivery ( $P = 0.002$ ; odds ratio = 230; 95% CI: 8–889). There was no difference in the cesarean delivery rate between the groups (21% in the CEI group versus 17% in the PIEB group;  $P = 0.68$ ). Longer labor was associated with an increased risk of instrumental delivery ( $P < 0.001$ ; odds ratio = 4.8; 95% CI: 1.9–11.8).

Total levobupivacaine and sufentanil consumption, number of patients requiring additional PCEA boluses, and mean number of PCEA boluses per patient are reported in Table 2. The hazard ratio for CEI versus PCEA for requiring a PCEA bolus was 5.0 (95% CI: 2.1–11.8;  $P < 0.001$ ). None of the patients required anesthesiologist-delivered manual boluses except those administered for instrumental vaginal delivery. Labor pain, as assessed by hourly VAPS score (data not shown), was similar in both groups and all scores at all times were <20 mm.

## DISCUSSION

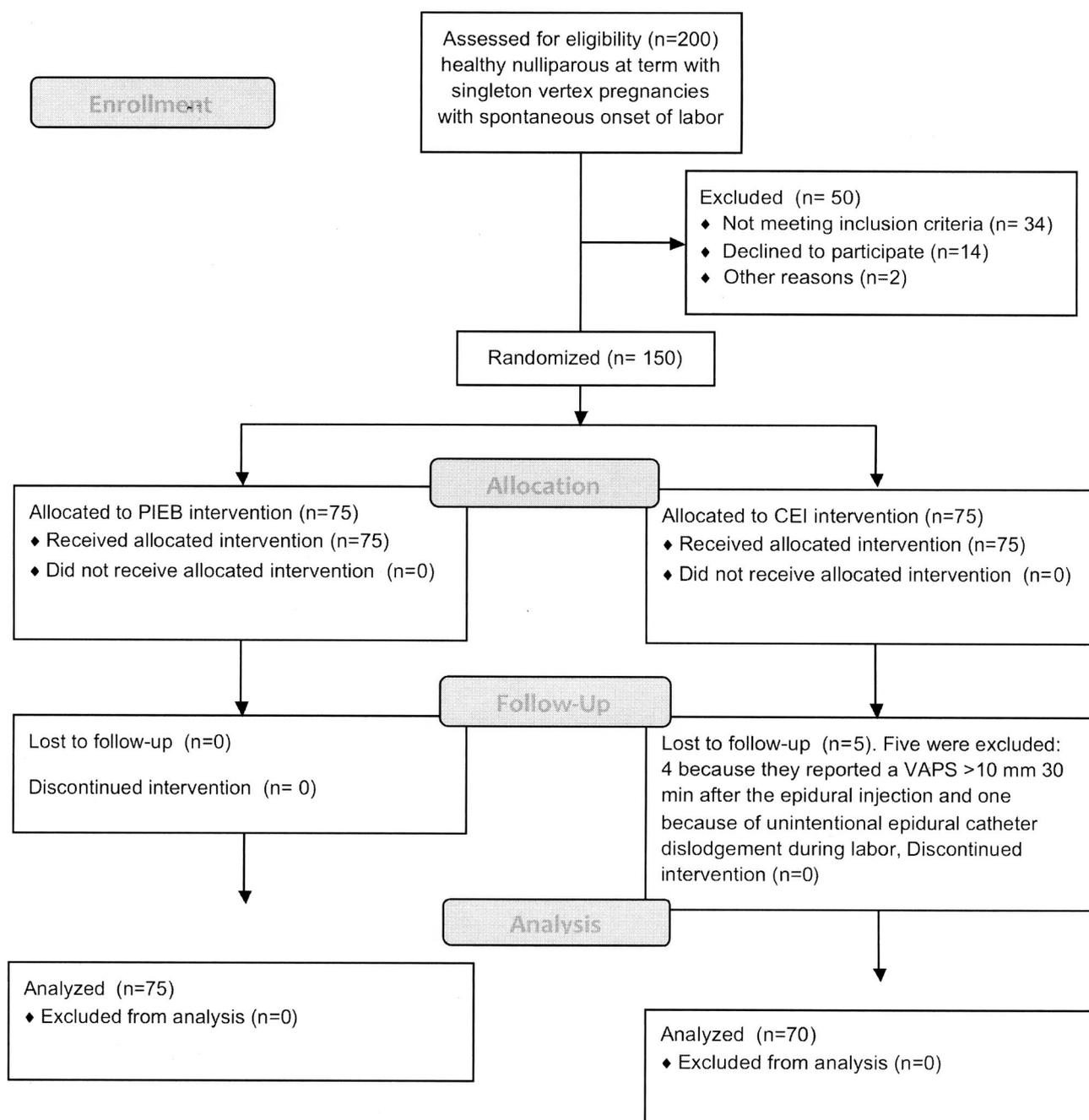
The important finding of this study was that PIEB resulted in less motor block during labor and at full cervical dilation, and was also associated with a lower incidence of instrumental

F1,T1

F2

T2

## CONSORT 2010 Flow Diagram



**Figure 1.** CONSORT (Consolidated Standards of Reporting Trials) flow diagram. PIEB = programmed intermittent epidural anesthetic bolus; CEI = continuous epidural infusion; VAPS = visual analog pain scale.

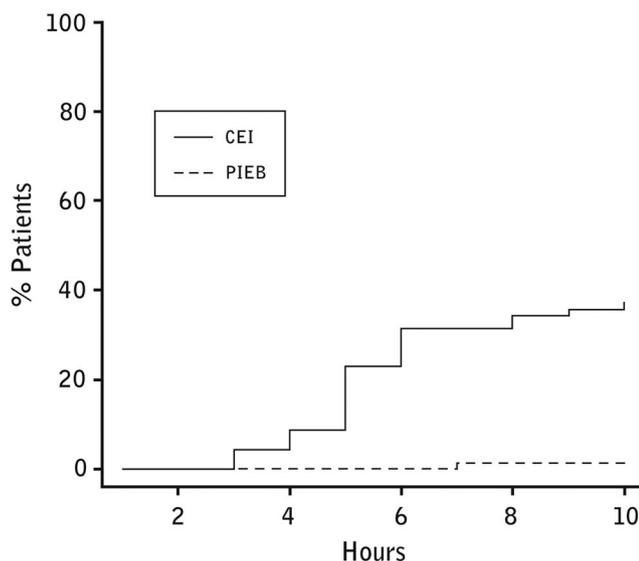
vaginal delivery compared with CEI, while providing equivalent labor analgesia. We also observed that PIEB was associated with less analgesic solution consumption, fewer requests for additional PCEA boluses, and longer time to first epidural bolus request. These results are consistent with those of previous studies.<sup>1,4-6</sup> The incidence of motor block and of operative delivery observed in our study sample with CEI was comparable to that reported by Beilin et al.<sup>10</sup> with the administration of a similar epidural regimen.

Previous studies comparing PIEB with CEI did not demonstrate any differences in motor block or mode of delivery. We observed that motor block tends to develop after a few hours; therefore, we have hypothesized that the lack of observation of motor block in previous studies is likely attributable to insufficient time to observe its development. Wong et al.<sup>4</sup> compared PIEB and CEI, both with PCEA, but they studied parous women undergoing induction of labor. These women generally have relatively short

**Table 1. Subject and Labor Characteristics**

	CEI (n = 70)	PIEB (n = 75)	P value
Age (y)	27 ± 5	29 ± 5	<0.01
Weight (kg)	72 ± 9	74 ± 11	0.2
Height (cm)	164 ± 6	165 ± 6	0.2
Gestational age (wk)	38.7 ± 0.7	38.9 ± 0.7	0.2
Cervical dilatation at epidural request (cm)	2.0 (1.0–3.0)	2.0 (2.0–3.0)	0.6
Duration of labor analgesia (min)	332 (318–380)	335 (326–358)	0.9

Data are presented as mean ± SD or median (interquartile range) (cervical dilatation) or median (95% confidence interval) (duration of labor analgesia). CEI = continuous epidural infusion; PIEB = programmed intermittent epidural bolus.



**Figure 2.** Percentage of patients from programmed intermittent epidural bolus (PIEB) or continuous epidural infusion (CEI) groups who had any motor block versus time after induction of labor analgesia. Data were censored for delivery. The groups were significantly different,  $P < 0.001$ .

**Table 2. Labor Analgesia**

	CEI (n = 70)	PIEB (n = 75)	P value
Total dose of levobupivacaine (mg)	37 (31–44)	31 (25–38)	0.001
Total dose of sufentanil ( $\mu$ g)	28 (24–34)	25 (20–30)	0.009
Patients requiring PCEA boluses (n)	28	6	<0.001
PCEA boluses for each patient (n)	1 (1–2)	1 (1–1)	<0.001

Data are presented as median (interquartile range) or number. CEI = continuous epidural infusion; PCEA = patient-controlled epidural analgesia; PIEB = programmed intermittent epidural bolus.

labors. Chua and Sia<sup>5</sup> reported a very low incidence of motor block in their study of nulliparous parturients, but they terminated their study when patients requested supplemental analgesia (on average after 4 hours), and therefore they were unable to observe any motor block. Lim et al.<sup>6</sup> studied programmed intermittent boluses versus CEI. They ended their study when the parturient complained of breakthrough pain and reported no motor block

at that time. It is likely that at the time of analgesic request, any motor block, if present, had already resolved. Fettes et al.,<sup>15</sup> in comparing programmed intermittent bolus administration with continuous infusion, reported a frequent incidence of motor block in both groups with no difference in motor block between groups, although the trend was toward less motor block in the intermittent bolus group. However, they used a higher local anesthetic concentration (ropivacaine 0.2%) than other studies, and this may have masked differences between the groups.

Another reason for the difference in results among studies is that some of the previous studies used different local anesthetic concentrations and total anesthetic dose from those used in our study. Furthermore, the scale we used to evaluate motor block is more sensitive than that used in previous studies,<sup>9</sup> and therefore the probability of diagnosing minor degrees of motor block was probably greater in our patients. In addition, the primary end point of previous studies was not motor block or mode of delivery, and therefore previous studies were not adequately powered to address these issues. Finally, we used an epidural rather than a subarachnoid initial loading dose,<sup>4–6</sup> and we set the PIEB pump to deliver a larger volume of local analgesic solution at longer time intervals relative to previous studies.<sup>4,5</sup>

In our study, we noted a lower incidence of instrumental vaginal delivery in parturients receiving PIEB compared with CEI. Recently, Leo et al.<sup>16</sup> also reported a trend toward a decreased incidence of instrumental vaginal delivery with automated intermittent boluses when compared with CEI, but, unfortunately, this result did not reach statistical significance, most likely because of the small sample size. In addition, Leo et al.<sup>16</sup> did not report the incidence of motor block, nor did they correlate motor block with instrumental delivery.

It is hypothesized that excessive motor block caused by the epidural local anesthetic is undesirable because it may lead to decrease of pelvic muscle tone and difficulties in internal rotation of the fetal head, and therefore to a potential increase in the incidence of instrumental vaginal delivery, although this assertion remains unproven.

In our study, parturients who had longer labors and motor block at full cervical dilation had a greater risk of instrumental delivery. Our results suggest that PIEB, by reducing the incidence of motor block, contributes to reduction in instrumental deliveries in nulliparous women.

Although local anesthetic consumption was higher in the CEI group, and we observed a difference in motor block between parturients receiving PIEB and CEI, the dose difference between groups was modest. Therefore, we suggest that the increased frequency of motor block in parturients receiving CEI cannot merely be explained by the larger local anesthetic dose. It is hypothesized that the reason for the analgesic success of intermittent boluses compared with continuous administration may be related to differences in the dispersion of solutions in the epidural space. Solutions injected into the epidural space tend to spread more evenly when injected as a bolus, as compared with a continuous infusion.<sup>2,3</sup> We have hypothesized that differences in the dynamics of nerve block with intermittent or continuous infusion administration may contribute to the explanation of our findings.<sup>17</sup>

Analgesia is produced by the movement of local anesthetic from the extraneural space into the nerve along a diffusion gradient. Over time, the extraneural concentration equals the intraneural concentration of local anesthetic, establishing a steady state. Nerve blockade is eventually overcome when the intraneural concentration exceeds the extraneural concentration (which will have been noticeably reduced by dispersion, dilution, tissue binding, and absorption) and the diffusion gradient is reversed. Susceptibility to local anesthetic depends on blocking a critical length of the nerve fiber. Thick, long-internode motor fibers have twice the critical blocking length of thin, short-internode pain fibers. Therefore, if low concentrations of local anesthetic are given in intermittent boluses, because in the above situation, blockade of motor fibers is unlikely because the total amount of local anesthetic inside the nerve is insufficient. However, in the case of continuous infusion, not only is the extraneural concentration of local anesthetic generally persistently higher than in the intraneural space, the total concentration inside the nerve is increased, thus reaching the threshold for motor fiber block. This may explain the frequent occurrence and intensification of motor block during continuous infusion.

One limitation of our study is that we assessed motor blockade of the lower extremities. If motor block adversely affects mode of delivery, it is likely that pelvic (sacral) and abdominal motor block, and not lower extremity block, is more important. However, measuring pelvic tone is difficult to accomplish clinically, so we chose to measure lower extremity motor block, as do most investigators, as a surrogate for pelvic muscle blockade. Another limitation of our study is that the decision to perform an instrumental vaginal delivery is made by individual obstetricians whose practices may vary. However, we believe that bias is unlikely because both the women and the obstetricians were unaware of the study group assignment. A further limitation of our study was that the PIEB dose was administered at the end of the first hour and therefore local anesthetic and sufentanil consumption were slightly higher in the CEI group because they were always ahead by study design. We also did not assess the extent of sensory blockade and therefore we were not able to determine the relationship between extent of sensory block and the occurrence of motor block, if any.

In summary, we found that in nulliparous women with spontaneous onset of labor, the maintenance of epidural analgesia with PIEB compared with CEI resulted in less motor block during labor and at full cervical dilation, and was also associated with a lower incidence of instrumental vaginal delivery. ■■

#### DISCLOSURES

**Name:** Giorgio Capogna, MD.

**Contribution:** This author helped design the study, conduct the study, analyze the data, and write the manuscript.

**Attestation:** Giorgio Capogna has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.

**Name:** Michela Camorcia, MD.

**Contribution:** This author helped design the study, conduct the study, analyze the data, and write the manuscript.

**Attestation:** Michela Camorcia has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**Name:** Silvia Stirparo, MD.

**Contribution:** This author helped design the study, conduct the study, and write the manuscript.

**Attestation:** Silvia Stirparo has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**Name:** Alessio Farcomeni, PhD.

**Contribution:** This author helped design the study, analyze the data, and write the manuscript.

**Attestation:** Alessio Farcomeni has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.

**This Manuscript was Handled by:** Cynthia A. Wong, MD.

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## AUTHOR QUERIES

### AUTHOR PLEASE ANSWER ALL QUERIES

1

AQ1— In the sentence beginning “Therefore, if low concentrations ...,” please clarify meaning, particularly “because in the above situation.”

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