

Analgesic efficacy of programmed intermittent epidural bolus vs patient-controlled epidural analgesia in laboring parturients

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Abstract

Background and Aims: Programmed intermittent epidural boluses (PIEB) may produce more extensive spread of epidural bolus rather than continuous epidural infusion (CEI). Previous studies compared PIEB with CEI and concluded that PIEB shows better outcome when combined with patient controlled epidural analgesia (PCEA), but these studies lack any comparison between PCEA and PIEB in the absence of CEI.

Material and Methods: In this open labeled, prospective, randomized, controlled study 50 parturient were randomly assigned to two groups of 25 each. Group 1 received PCEA bolus of 5 ml (0.1% levobupivacaine plus 2mcg/ml fentanyl) with 15 min lockout interval with provision of rescue clinician bolus of 5 ml of same drug for breakthrough pain. Group 2 received physician-administered PIEB with same parameters as Group 1. The primary outcome was to assess total consumption of levobupivacaine plus fentanyl mixture, in PIEB vs. PCEA group, corrected for duration of labor (ml/h) and secondary outcomes included pain score, maternal satisfaction, maternal, and neonatal characteristics.

Results: The hourly mean drug consumption in the PCEA group was significantly lower as compared with the physician-administered PIEB group (5.46 ml/h, SD 2.01 vs. 6.55 ml/h, SD 1.28; $P = 0.03$). The median total number of rescue boluses consumed were less in the PCEA group when compared with the PIEB group (0 vs. 1; $P < 0.001$). There was no significant difference between groups with regard to pain scores, maternal hemodynamics, maternal and fetal outcome and adverse effects.

Conclusion: PCEA may be better than physician-administered PIEB in providing effective labor analgesia with comparable safety.

Keywords: Labor analgesia, patient-controlled epidural analgesia, programmed intermittent epidural bolus, randomized controlled trial

Introduction

Labor pain is one of the most painful experiences for a woman. It causes significant respiratory and cardiovascular changes. Labor pain is dynamic as well as variable and various methods have been chosen to relieve labor pain.^[1] There are variety of modalities available to provide pain relief during labor but neuraxial analgesia

is considered the gold standard due to its proven efficacy and flexibility with maternal satisfaction.^[2] Continuous epidural infusion (CEI), patient controlled epidural analgesia (PCEA) with basal infusion, Automated mandatory boluses (AMBs), programmed intermittent epidural boluses (PIEBs) and computer integrated PCEA (CIPCEA) have been used to maintain analgesia for the duration of labor.

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	DOI: 10.4103/joacp.JOACP_210_20

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How to cite this article: Meena A, Mitra S, Singh J, Saroa R, Takker N. Analgesic efficacy of programmed intermittent epidural bolus vs patient-controlled epidural analgesia in laboring parturients. *J Anaesthesiol Clin Pharmacol* 2022;38:178-83.

Submitted: 03-May-2020

Revised: 07-Jun-2020

Accepted: 29-Nov-2020

Published: 28-Jul-2022

The aim is to provide safe and effective analgesia to the mother and to make her childbirth experience satisfactory with minimal or no side effects. It has been acknowledged that intermittent bolus technique offers multiple theoretical benefits over PCEA alone or CEI plus PCEA.^[3] There is more uniform spread of analgesic solutions in the epidural space when they are injected as boluses compared to continuous administration. However, the actual results of few studies do not provide an unequivocal superiority of PIEB over PCEA or CEI plus PCEA. The most recent meta-analysis concluded that PIEB plus PCEA group had better outcome than compared to CEI plus PCEA group, but additional studies need to be conducted to consistently demonstrate an improvement in the maternal and fetal obstetric outcomes.^[4]

Thus, the present study was designed to compare the two techniques of physician-administered PIEB and PCEA on the hourly average consumption of epidural levobupivacaine and fentanyl mixture (ml/h) corrected over duration of labor, pain score, maternal satisfaction, maternal, and neonatal outcome.

Material and Methods

This was an open labelled, prospective, randomized, controlled study conducted at a tertiary care medical teaching institute in North India. After obtaining ethical approval for the study from Institutional Ethics Committee and trial registration with the Clinical Trial Registry of India (CTRI Registration No.CTRI/2018/03/012384, March 2018) and after obtaining written informed consent, 50 parturients were enrolled for the study. The inclusion criteria were: American Society of Anesthesiologists (ASA) grade I and II parturients with age >18 years, requesting for epidural analgesia for labor and able to use PCEA pump with baseline pain score >30 (on a 0-100 visual analog scale [VAS]), primigravida with spontaneous onset of labor at ≥ 36 weeks, cervical dilation ≤ 5 cm and single live fetus with cephalic presentation. Primigravida were chosen because the duration of labor and other parameters vary between primi and multigravida. Exclusion criteria for the study were: refusal by parturient, parturients who had received parenteral opioids in the last 4 hours, systemic and local sepsis, deranged coagulation profile, parturients having multiple pregnancies and premature labor, obstetric complications (premature rupture of amniotic membranes), chorioamnionitis, HELLP syndrome, noncephalic presentations, allergy to study drugs (i.e., levobupivacaine and fentanyl).

The patients enrolled for the study were randomized into two groups of 25 each (CONSORT flow diagram shown

in Figure 1) using computer generated random number table using coded sealed opaque envelope. The parturient was placed in sitting position and combined spinal epidural (CSE) was performed in L_{3,4} or L_{4,5} space with 18G Tuohy's needle, using loss of resistance to air technique. A 27G Whitacre spinal needle was used and after confirming the free flow of CSF, 0.5 ml of 0.5% hyperbaric bupivacaine (2.5mg) was injected intrathecally. This was noted as the start of the study period. Epidural catheter of 20G was inserted and 4cm was left in epidural space. All patients were connected to PCEA (Master PCA pump, Fresenius Kabi, Finland).

Group 1 received PCEA bolus of 5 ml (0.1% levobupivacaine plus 2 mcg/ml fentanyl) with 15 min lockout interval with provision of rescue clinician bolus of 5 ml of same drug for breakthrough pain. Group 2 received physician-administered PIEB of 5 ml (0.1% levobupivacaine plus 2 mcg/ml fentanyl) hourly with provision of PCEA bolus of 5 ml with lockout interval of 15 min of same drug as rescue analgesic for breakthrough pain.

Patient characteristic data, including age, weight, height, and baseline investigations were recorded. After shifting the patient to clean labor room operation theatre intravenous access was secured and patient was preloaded with ringer lactate solution, multichannel monitors were attached and baseline heart rate (HR), electrocardiogram (ECG), non-invasive blood pressure (NIBP) and oxygen saturation (SPO₂), fetal heart rate (FHR) were continuously monitored throughout the study period.

In Group 1, all the parturients received PCEA pump after positioning the patient sitting (Master PCA pump, Fresenius Kabi, Finland). The patients were provided with a hand-held device and instructions were given to self-administer a PCEA bolus (5 ml of 0.1% levobupivacaine + 2 mcg/ml fentanyl) by pressing a button on the device once they experience a recurrence of pain (VAS more than 30). They were counseled to activate a PCEA bolus as and when necessary. Lockout interval was set at 15 min. First administered patient-activated PCEA bolus was noted whenever patient complained pain after the spinal anesthesia. If the parturient felt inadequate analgesia (VAS more than 30) even after activation of PCEA bolus, then there was provision of rescue analgesic in the form of physician-controlled bolus of 5 ml of same drug.

In Group 2 (PIEB with PCEA), patients received physician-controlled programmed intermittent boluses of (0.1% levobupivacaine plus 2 mcg/ml fentanyl) 5 mL hourly. The first PIEB dose was delivered when the parturient complained pain (VAS more than 30) for the first time after the subarachnoid block and the time to the same was noted

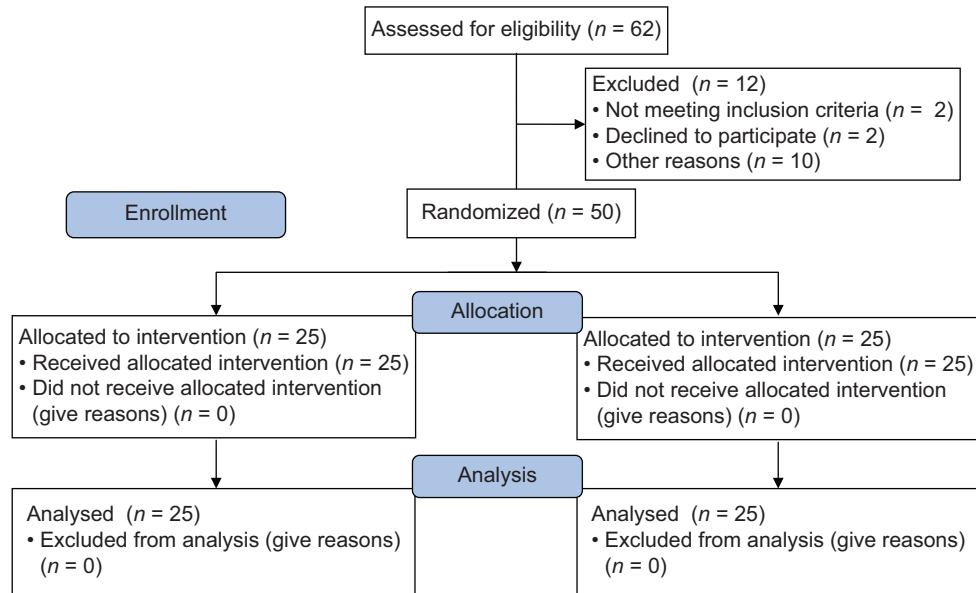


Figure 1: CONSORT Flow Chart

on the prescribed proforma. Subsequently, PIEB doses were administered at hourly interval during the course of labor. There was provision of rescue analgesia (VAS more than 30) in the form of PCEA bolus of 5 ml drug (0.1% levobupivacaine + 2 mcg/ml fentanyl) with 15 min lockout interval during the course of labor.

The primary outcome of the study was total consumption of levobupivacaine plus fentanyl mixture, in PIEB vs. PCEA group, corrected for duration of labor (ml/h). Secondary outcome variables were maternal satisfaction (on 0-100 VAS), visual analog pain score (VAS based on a 0-100 mm scale, 0 mm = no pain and 100 mm = worst pain imagined), sensory and motor block characteristics, hemodynamic parameters of mother fetal heart rate, duration of second stage of labor, mode of delivery, Apgar scores, and adverse effects.

From our own previous data on 30 patients undergoing labor epidural analgesia with PCEA in our hospital, it was seen that the mean hourly consumption was 8.40 ml/h, with a standard deviation (SD) of 2.0. It was decided that a 20% reduction in hourly consumption of neuraxial analgesic combination would be considered as clinically meaningful difference, yielding a value of 6.72 ml/h with SD of 2.0 as the mean hourly neuraxial drug consumption in the intermittent mandatory bolus infusion group. Thus, for this study, sample size analysis with the above assumption and with a β error of 0.20 (i.e. power of 80%) and an alpha error of 0.05 demonstrated that a sample size of 23 per group would allow us to detect a 20% difference in total epidural drug combination volume required per hour. To allow for slight oversampling, it was decided to have a total sample size of 50 patients, with 25 patients per group.

All data was analysed using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, version 17.0 for Windows). Means were compared using Student's t-test for independent groups if the data was normally distributed (determined using Kolmogorov-Smirnov test) and Mann-Whitney U-test if the data that was not normally distributed. Proportions were compared using Chi square or Fisher's exact test whichever applicable. Pain VAS scores in the two groups were compared using two-way ANOVA with post-hoc Scheffe's test. Qualitative or categorical variables were described as frequencies and proportions. Statistical tests were two-sided and performed at a significance level of $\alpha = 0.05$.

Results

A total of 50 parturients were enrolled, 25 in each group. Both the groups were similar with respect to patient characteristics profile [Table 1]. Both the groups were comparable with respect to baseline investigations and results were found to be statistically non-significant.

Regarding the primary outcome, the total hourly consumption of levobupivacaine-fentanyl combination was significantly less in the PCEA group (5.46 ± 2.01 ml/h) when compared with PIEB group (6.55 ± 1.28 ml/h) with P value of 0.03 [Table 2]. The total number of boluses corrected for duration of labor was less in the PCEA group (Mean 1.04, SD 0.80-1.34) when compared to PIEB group (mean 1.32, SD 1.055-1.455; $P = 0.05$). The median total number of rescue boluses consumed was statistically significantly less in the PCEA group (0, with interquartile range [IQR] 0) when compared with the PIEB group (1.00, with IQR 0-1; $P < 0.001$).

In our study, onset time of analgesia was started when drug was administered intrathecally to the pain VAS score <30, the median onset time was comparable (28 min with IQR 18-49.5 in PCEA group, and 25 min with IQR 17-38 in PIEB group, with *P* value = 0.197). The mean pain VAS score was comparable between both the groups. Compared with the pre-treatment score, mean VAS score was lower at subsequent intervals in both the groups.

The median duration of labor was comparable in the two groups for PCEA and PIEB group respectively (273 minutes with IQR 156-539, and 244 minutes with IQR 163-382; *P* = 0.42). Fetal heart rate was comparable or within the normal range, and the differences were not statistically significant. After delivery, irrespective of the mode, i.e., normal vaginal delivery or instrumental, Apgar scores at 1 min. and 5 min. showed no statistical difference between two groups. The changes in mean heart rate, systolic and diastolic blood pressure in both groups were minimal and non-significant between the groups. Similarly, time to sensory and motor blockade was comparable between the groups [Figure 2]. No difference in global maternal satisfaction mean score was observed between both the groups (99.2 ± 2.38, 98.4 ± 3.78; *P* = 0.59).

Adverse effects were common but minor in this study and consisted mainly of vomiting, shivering and hypotension. There were non-significant differences in occurrence of side effects between the two groups [Table 3]. Both the groups were comparable in respect to severity and incidence of motor blockade.

Table 1: Patient characteristics

Characteristics	Group 1(PCEA)	Group 2(PIEB)	<i>P</i>
Age	26.72±2.60	26.76±3.57	0.964
Height (cm)	157.32±11.07	156.56±13.40	0.828
Weight (kg)	70.20±14.20	69.84±12.62	0.925
Body mass index	28.39±5.01	28.55±4.26	0.905

Values expressed as mean±SD

Table 2: Primary and secondary outcomes in the two groups

OUTCOME MEASURE	GROUP 1 (PCEA) (n=25)	GROUP 2 (PIEB) (n=25)	<i>P</i>
Primary outcome			
Total drug consumption (ml/h)	5.46±2.01	6.55±1.28	0.03
Number of boluses (bolus/h)	1.04 [0.80-1.34]	1.32 [1.05-1.45]	0.05
Secondary outcomes			
Mode of delivery			
Normal vaginal delivery	21 (84%)	21 (84%)	1.00
Instrumental	4 (16%)	4 (16%)	
Onset time of analgesia, min	28 [18-49.5]	25 [17-38]	0.19
Maternal satisfaction, VAS 0-100	99.2±2.38	98.4±3.78	0.59

Values expressed as mean±SD, number (%), or n=number of patients or median with interquartile range [IQR]. VAS: visual analog scale

Discussion

This study demonstrated the decreased requirement of local anesthetic and opioid consumption in labor analgesia of PCEA group compared to PIEB group in combined spinal epidural analgesia in laboring parturients. This study also showed that there is decreased average hourly consumption of drug, total number of boluses/h, total number of rescue boluses in laboring parturients using PCEA. The findings in the present study are in contrast with the general notion and recent meta-analyses that PIEB is more advantageous than PCEA alone or CEI plus PCEA.^[3-5] However, there is wide variability in the actual methodology in terms of drugs, doses, programming, timing, rescue provisions, PIEB bolus size and interval, PIEB start time delay period, and patient-controlled

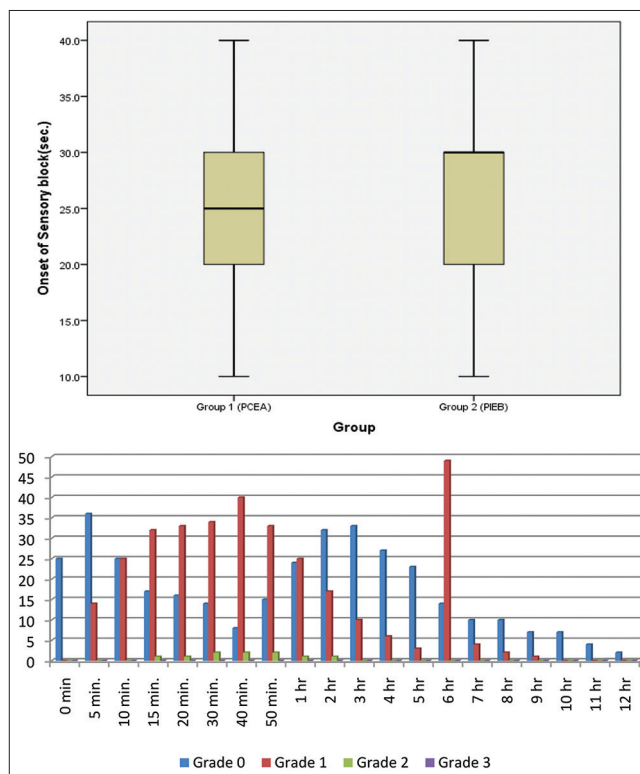


Figure 2: Sensory and motor block in the two groups

Table 3: Adverse effects

Adverse effects	GROUP 1(PCEA) (n=25)	GROUP 2 (PIEB) (n=25)	P
Pruritus	0 (0%)	0 (0%)	-
Nausea	0 (0%)	0 (0%)	-
Vomiting	1 (4%)	1 (4%)	1.00
shivering	0 (0%)	2 (8%)	0.49
Urinary retention	0 (0%)	0 (0%)	-
Fever	0 (0%)	0 (0%)	-
Hypotension	1 (4%)	0 (0%)	1.00
Fetal bradycardia	0 (0%)	0 (0%)	-

epidural analgesia bolus size and lockout time, etc. All these can influence the efficacy of PIEB used for epidural labor analgesia.

In an earlier study, Boutros *et al.* found that local anesthetic requirement was higher in the PCEA group than in the bolus group, conversely Gambling *et al.* and Vandermeulen *et al.* found that PCEA and intermittent bolus techniques resulted in the administration of comparable doses of local anesthetics.^[6,7]

Vandermeulen and Kumar *et al.* reported higher local anesthetic consumption in PIEB group compared to PCEA group.^[7,8] Halpern and Carvalho evaluated six studies comparing various patient- controlled epidural analgesia schedules and found greater distribution of anesthetics in the epidural space with improved quality of analgesia when large bolus doses used with greater lockout intervals. However, there were no benefits regarding the number of rescue bolus doses.^[9] Another recent study by Ojo *et al.* found no significant difference in PCEA consumption when PCEA is used in conjunction with PIEB vs. CEI. They did not find any improved outcomes with PIEB compared to CEI except for less motor blockade in the PIEB group.^[10] Similarly, in the present study wetoo have demonstrated the role of PIEB no better than PCEA in providing effective analgesia.

The latest published study in this area compared PIEB plus PCEA with only PCEA in a two-centre RCT and found that PIEB plus PCEA worked better than PCEA alone in reducing breakthrough pain, though the maternal satisfaction remained comparable in both the groups.^[11] However, the authors admitted that their results could be due to the large-bolus PIEB used in their index group (programmed bolus of 10 ml of ropivacaine 0.12% with sufentanil 0.75 µg/ml every hour, with on-demand patient-controlled epidural analgesia boluses of 5 ml with a 20 min lockout) compared with the low-bolus PCEA (5 ml bolus with a 12 min lockout interval) so that the PIEB plus PCEA group received significantly higher total amounts of local anesthetic compared to the PCEA only group (median 55 vs. 35 ml respectively, $P < 0.001$), and

outlined the need for further study in which the PIEB bolus volume is similar to the PCEA bolus volume.

While comparing secondary outcome variables, there was no significant difference in maternal VAS scores for pain, maternal hemodynamics, and mode of delivery between the study groups. A recent Cochrane meta-analysis showed that the duration of 1st stage of labor was increased but was statistically not significant and the second stage of labor although prolonged with epidural, but that did not affect the neonatal outcome.^[12] In another study Wang *et al.* found that utilization of labor epidural analgesia increased the vaginal delivery rate, decreased the cesarean section rate without any adverse effect on neonatal outcome.^[13] In the present study neither any prolongation of labor nor any significant increase in the rate of instrumentation or the side effects pertaining to epidural analgesia were observed.

There was no statistical difference between the Apgar scores at 1 min. and 5 min. between the two groups. Immediate physical condition of the neonate was also assessed; none of them required naloxone administration, resuscitation efforts or presented with Apgar score less than 7.

Side effects were comparable in both groups. None of the patients had incidence of nausea, pruritus, fever, urinary retention, postdural puncture headache, nerve injury and fetal bradycardia, whereas incidence of vomiting, shivering, hypotension were comparable and not significant.

The strengths of the study are that it was a prospective, randomized clinical trial. Sample size was calculated and adequate number of patients was enrolled for the study. Also, strict inclusion and exclusion criteria were followed during patient selection. The present study had some limitations too, blood level assay of the two drugs were not done, and secondly the PIEB was physician-administered. One might speculate that physician-administered PIEB might affect the dynamics of the drug spread in the epidural space. However this does not invalidate the findings of the study.

In conclusion, this randomized controlled trial demonstrated that PCEA as compared to physician-administered PIEB has dose sparing effect on levobupivacaine-fentanyl combination in combined spinal-epidural analgesia in laboring parturients. This study also showed that there is decreased average hourly consumption of drug, total number of boluses per hour, total number of rescue boluses in laboring parturients using PCEA. Both the groups were comparable for pain, maternal satisfaction, fetal outcome, mode of delivery, maternal hemodynamic parameters, duration of labor, and side effect profile. All in all, the present study showed PCEA may be

better than physician-administered PIEB in providing effective labor analgesia with comparable safety.

Financial support and sponsorship
Nil.

Conflicts of interest

There are no conflicts of interest.

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