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Programmed intermittent epidural bolus, an ideal method for labor analgesia: A randomized controlled trial

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Running title: Epidural injection for labor analgesia

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Author contributions

Doyeon Kim: This author helped to concept and design the study, data collection, data analysis and interpretation, writing, drafting, and revising the manuscript.

Jeayoun Kim: This author helped to collect data, data analysis, and interpretation and revising the manuscript.

Hyeonju Choo: This author helped to analyze data and drafting the manuscript.

Duck Hwan Choi: This author helped to provide the concept of the idea, design the study, data collection, data analysis and interpretation, drafting and revising the manuscript, and roll as a research group leader and supervision of the work.

All authors approved the manuscript and agreed to be accountable for all aspects of the work.
Programmed intermittent epidural bolus, an ideal method for labor analgesia: a randomized controlled trial

Running title: Epidural injection for labor analgesia
Abstract

Background Although programmed intermittent epidural bolus (PIEB) is effective for labor analgesia, appropriate flow rate has not established. Thus, we investigated the analgesic effect according to the epidural injection flow rate.

Methods Nulliparous women scheduled for spontaneous labor were enrolled in this randomized trial. After injection of intrathecal 0.2% ropivacaine 3 mg with fentanyl 20 mcg, participants were randomized to three study groups. Patient-controlled epidural analgesia at 10 mL/hour was given as follows (0.2% ropivacaine 60 ml, fentanyl 180 mcg, and 0.9% saline 40 ml): continuous (n=28, 10 mL/hour), PIEB (n=29, a rate of 240 mL/hour every hour), or manual (n=28, a rate of 1200 mL/hour every hour). The primary outcome was hourly consumption of epidural solution. The time interval from labor analgesia to the first breakthrough pain was investigated.

Results The median [interquartile range] hourly consumption of epidural anesthetics was significantly different among the groups (continuous: 14.3 [11.4, 19.6] mL; PIEB: 9.4 [7.1, 10.7] mL; manual: 10.0 [9.5, 11.8] mL; p < 0.001). Time to the breakthrough pain was longer in PIEB than others (continuous: 78.5 [35.8, 185.0] min, PIEB: 215.0 [92.0, 433.0] min, and manual: 73.0 [4.5, 198.0] min, p =0.027).

Conclusion We found that PIEB provides adequate labor analgesia. Excessively high flow rate of epidural injection was not essential for labor analgesia.

Keywords: Analgesia, Epidural; Analgesia, Labor; Anesthesia, Conduction; Labor, Obstetric; Patient-Controlled; Pregnancy
Introduction

Epidural analgesia is considered as the gold standard for labor analgesia. Although provider-given manual epidural infusion was classically performed as labor analgesia, with the advances of technology, new methods such as continuous epidural infusion and programmed intermittent epidural bolus (PIEB) have been introduced. Both are widely used in clinical situation for labor analgesia in combination with patient’s epidural bolus.[1]

PIEB is a method of automatically injecting local anesthetic into the epidural space.[2] It provides superior analgesia and decreases motor blockade compared with conventional continuous epidural infusion.[3] It is known that PIEB has an effective analgesic effect because it more uniformly distributes the local anesthetic in the epidural space with a large volume and high flow rate.[4] However, there is no standard for the appropriate flow range of PEIB. Although previous study reported that the higher the infusion rate, the higher pressure was generated during PIEB,[5] Lange et al. showed that the small difference in epidural infusion flow rates (100 mL/hour vs 300 mL/hour) did not contribute to satisfactory labor analgesia.[6] Furthermore, since it is difficult to provide a high flow rate above a certain level due to the pressure limitation of the machine itself, additional research is needed to establish a satisfactory level of epidural infusion flow rate.

Based on this, we hypothesized that high-flow epidural bolus infusion of local anesthetics would be efficient than low-flow bolus infusion during labor analgesia. Thus, we aimed to compare the effect of labor analgesia by epidural analgesics infused at different flow rate.
Materials and Methods

Ethics
This randomized, parallel-group, single blind study was ethically approved by the Institutional Review Board of our institute and was registered in the clinical trial registry prior to recruitment of the first participant. Written informed consent was obtained from all participants before enrolment in this study. All methods were performed in accordance with the Declaration of Helsinki and its revisions.

Patients
Nulliparous women with gestational age ≥ 36 weeks, single-tone pregnancy, American Society of Anaesthesiologist physical status I or II scheduled for spontaneous or induced vaginal delivery with a cervical dilatation between 2 and 5cm and regular contractions occurring every 3-5 minutes were assessed for eligibility and included between November 2019 and December 2020. Exclusion criteria were women received opioids or sedatives, received opioid within 4 hours previous labor analgesia, hypersensitivity, or allergy to local ropivacaine or fentanyl, preeclampsia, and premature rupture of membrane.

Randomization and blindness
One statistician who was not involved in this study generated a random allocation sequence. The participants were randomly assigned to one of the three study groups under a computer-generated randomization sequence: continuous, PIEB, or manual group. Randomization and group allocation were performed at a 1:1:1 ratio with a bock size of 3. Group assignment was performed using the sealed, opaque envelope technique by one of the authors. The investigator was blinded to the assigned group.
Study protocol

Combined spinal epidural analgesia (CSE) procedure for labor analgesia was performed by residents under the supervision of an experienced obstetrical anesthesiologist. Prior to the procedure, patient’s intravenous route was secured and standard monitoring was applied including blood pressure, pulse, oxygen saturation, respiration rate, fetal pulse rate, and uterine contractions. At the L3–4 interspace with the patient in the lateral decubitus position, lumbar puncture was performed using a 25-gauge Whitacre needle (Whitacre Needle, 25G x 3.50IN TW, BD, New Jersey, USA). After confirming the free flow of cerebrospinal fluid, intrathecal agents (0.2% ropivacaine 3 mg with fentanyl 20 mcg) were administered to relieve labor pain immediately. Then, the epidural space was located using a 17-gauge Tuohy needle at L 3-4 or L 4-5 level with the loss of resistance to air technique. An epidural catheter (FlexTip Plus Epidural Catheter Set, 19G, Arrow electronics, Colorado, USA) was inserted 5-6 cm into the epidural space and confirmed the position by negative aspiration for blood and CSF and flushed with 4 mg of 0.2% ropivacaine. All procedure was done by aseptic technique.

According to the assigned group, ambulatory infusion pump (Accumate 1200, Wooyoung meditech Co., LTD, Seoul, Korea), consisted with 0.2% ropivacaine 60 ml, fentanyl 180 mcg, and 0.9% saline 40 ml, was initiated. Prior to the start of this trial, ambulatory infusion pump device was tested using an infusion device analyzer (IDA 4 Plus Multi-Channel Infusion Device Analyzer, Fluke biomedical, Cleveland, USA) to confirm its applicability. patient controlled-epidural analgesia (PCEA) drugs were prepared by a nurse who did not relate to this trial.

The details of drug delivery protocol according to the assigned group were as followed:

- Continuous group: PCEA + basal continuous epidural infusion 10 ml/hour, started infusion 30 minutes after labor analgesia procedure.

When the bolus button was pressed by the patient, 5 mL of local anesthetics was injected. Basal
continuous epidural infusion continued regardless of the bolus dose.

- PIEB group: PCEA + programmed intermittent epidural boluses 10ml every hour (240 ml/hour), started infusion 60 minutes after labor analgesia procedure.

  When the bolus button was pressed by the patient, 5 mL of local anesthetics was injected and a programmed intermittent epidural bolus was injected after 15 minutes.

- Manual group: PCEA + provider-given intermittent epidural boluses 10ml every hour (1200 ml/hour), started infusion 60 minutes after labor analgesia procedure. For the participants in manual group, an experienced anesthesiologist injected 10 mL of the ropivacaine with fentanyl mixture at a constant rate for 30 seconds through an epidural catheter.

  When the bolus button was pressed by the patient, 5 mL of local anesthetics was injected. A provider-given epidural bolus was injected at set intervals regardless of the bolus dose.

Labor pain was measured using a 0–10 cm numerical rating scale (NRS: 0=no pain and 10=the worst pain imaginable). The participants were educated that PCEA bolus could be additionally used for labor analgesia. The breakthrough pain was defined as pain requiring bolus infusion of PCEA while receiving epidural anesthetics according to the assigned group. When the breakthrough pain with an NRS score ≥ 4 occurred during PCEA infusion, rescue medications were injected as follows: 0.2% ropivacaine 14 mg was administered to the epidural space. If the pain was not subsided, 1% lidocaine 50 mg was added. The delivery method was switched from vaginal delivery to Cesarean section in cases where failure to progress in labor occurred even after more than 4 hours of labor or when the mother requested it.

Patient's age, height, weight, body mass index (BMI), gestational age, cervical dilatation at the time of labor analgesia, total labor duration, any adverse effects associated with the labor analgesia (e.g., nausea, vomiting, numbness, paraplegia, post-dura puncture headache, local anesthetic systemic
toxicity), duration of second stage, incidence and NRS score of breakthrough pain, use of oxytocin, and preoperative blood pressure, heart rate, NRS score after labor analgesia procedure, conversion rate to Cesarean section, and patient’s satisfaction by Likert scale were also recorded.

Outcomes

The primary outcome was hourly consumption of epidural analgesics from the labor analgesia procedure to deliver among the three groups. The secondary outcomes were the difference in the time interval to the first breakthrough pain, NRS score for breakthrough pain, the degree of sensory and motor nerve blockade and NRS score at 4 hours after labor analgesia procedure among the three study groups. Considering the duration of intrathecal anesthetics which injected during the labor analgesia procedure, we investigated the degree of sensory and motor blockade 4 hours after labor analgesia procedure. Neonatal outcomes including birth weight and Apgar scores were also recorded.

The degree of sensory blockade was recorded using cold sensation and the degree of motor blockade was investigated by using the Breen-modified Bromage score (1= complete block, unable to move feet or knees; 2= almost complete block, only able to move feet; 3= partial block, just able to move below knees; 4= detectable weakness of hip flexion while supine, between scores 3 and 5; 5= no detectable weakness of hip flexion while supine but cannot stand due to hip weakness, full flexion of knees; and 6= being able to stand and perform a partial knee bend).[7]

Statistical Analyses

A power calculation was based on a previous study that investigated the effect of PCEA plus automated mandatory boluses (PIEB) for reducing the hourly consumption of local anesthetics during labor (mean ± standard deviation (SD): control group, 7.5 ± 2.0 mL vs PIEB group 6.5 ± 3.4 mL).[8] We hypothesized that the difference in hourly consumption of local anesthetic consumption among
the three groups was clinically significant when it was minimum of 1 mL. Thus, we calculated that
28 patients per group would give the study a power of 80% at a significance level of 5% under the
assumption that the difference in local anesthetics consumption among three groups was clinically
significant. Considering the dropout rate of 10%, a minimum of 31 patients in each group (total of
93) was required to participate in this study.

Continuous variables were expressed as the mean ± SD or median [interquartile range], while
normality was assessed by the Shapiro-Wilk test. Categorical variables were expressed as the number
(percentage). One-way ANOVA or Kruskal-Wallis test was used as appropriate to determine the
difference of continuous variables among the study groups, including hourly consumption of epidural
analgesics, time interval to the first breakthrough pain, NRS score for breakthrough pain after labor
analgesia, the degree of sensory and motor nerve blockade and NRS score at 4 hours after labor
analgesia procedure, and obstetric and neonatal outcomes. Categorical variables including the
incidence of breakthrough pain and mode of delivery were analysed using Pearson’s Chi-square test.
Partitioning chi-square test was applied for multiple pairwise comparisons. Bonferroni correction was
used to adjust p values in multiple comparisons. Statistical analyses were performed using SPSS
version 25 (IBM Inc., NY, USA), and p < 0.05 was considered to be statistically significant.
Results

A total of 96 parturient women were examined for eligibility and 3 of them were excluded for the following reasons: not meeting inclusion criteria (n=1), declined to participate (n=2). In addition, 8 women withdrew from this trial because they did not want to continue participating in the study. Finally, 85 participants were completed this trial: continuous group (n=28), PIEB group (n=29), and manual group (n=28) (Figure 1). When labor analgesia was performed, there was no difference in cervical dilation among the three study groups (continuous: 3 [3,3], PIEB: 3 [3, 3], manual: 3 [3. 3], respectively). All participants were using oxytocin. NRS before labor analgesia was comparable in all three groups (continuous: 6 [5, 8], PIEB: 6 [5, 7], manual: 5 [5, 6], respectively). Demographics data were similar among the study groups (Table 1).

There were no differences in the duration of PCEA application among the three groups (p = 0.285) (Table 2). However, the hourly consumption of epidural analgesics was significantly different among the three study groups (continuous: 14.3 [11.4, 19.6] mL; PIEB: 9.4 [7.1, 10.7] mL; manual: 10.0 [9.5, 11.8] mL; p < 0.001). There were statistical differences of the hourly consumption of epidural analgesics between continuous group and other groups (continuous vs PIEB, p < 0.001, PIEB vs manual, p = 0.413, continuous vs manual, p < 0.001, respectively) (Figure 2).

Participants requiring PCEA bolus infusion due to breakthrough pain were 22 (78.9%) in the continuous group, 19 (65.5%) in the PIEB group, and 14 (50.0%) in the manual group, respectively (p = 0.081). The NRS scores at the time of complaining of breakthrough pain were not significant among the three groups (continuous: 4.0 [3.8, 4.0], PIEB: 4.0 [3.0, 4.0], manual: 3.5 [3.0, 4.0], p = 0.195). The PIEB group expressed breakthrough pain after a significantly longer time than manual group (continuous: 78.5 [35.8, 185.0] min, PIEB: 200.0 [88.5,441.5] min, manual: 60.5 [37.3,162.0] min; p = 0.027). (Table 2).

Four hours after labor analgesia procedure, there were no differences in the degree of sensory and
motor blockade among the study groups (sensory blockade: \( p = 0.974 \), motor blockade: \( p = 0.224 \), respectively). There were two cases of motor nerve blockage 4 hours after infusion, 1 case in continuous group and 1 case in manual group. The NRS scores were not significantly different among the three groups at 4 hours after labor analgesia procedure (\( p = 0.066 \)). Obstetric and neonatal outcome were shown in Table 3. There was a statistical difference in mode of delivery among the three groups. (continuous: 18 [64%], PIEB: 27 [93%], and manual: 18 [64%], \( p = 0.021 \)). In pairwise comparisons, Mode of delivery did not show a significant difference according to the epidural injection methods (continuous vs PIEB: \( p = 0.069 \), PIEB vs manual: \( p = 0.081 \), manual vs continuous: \( p > 0.99 \)). Although three participants complained of numbness in the lower extremities immediately after labor analgesia, they recovered within 4 hours. There were two participants in the continuous group who required 0.2% ropivacaine 14 mg as an epidural rescue medication. No other adverse events occurred during the study period.
**Discussion**

This randomized clinical trial showed that PIEB or manual infusion of epidural analgesics effectively reduced the hourly consumption of epidural analgesics, rather than continuous epidural infusion in labor analgesia. In addition, the time taken to express the first breakthrough pain after labor analgesia procedure was significantly longer in the PIEB group than in the other groups.

Numerous studies demonstrated that intermittent epidural bolus injection provides superior labor analgesic effects than continuous infusion, reducing local anesthetic consumption and increasing maternal satisfaction.[8-13] A systematic review reported that larger bolus doses of dilute epidural anesthetics were required for superior analgesia.[14] In this context, Wong et al. demonstrated that administration of larger doses of epidural anesthetics at long time intervals reduces the consumption of bupivacaine and increases maternal satisfaction (2.5 mL/15 min vs 5 mL/30 min vs 10 mL/60 min).[15] In addition, they reported increased maternal satisfaction by using larger doses of epidural anesthetics at long time interval. Most previous studies on PIEB have mostly compared various bolus volumes and time intervals. However, studies comparing differences according to the flow rate of administered drugs are lacking.

Lange et al., who investigated the difference in the effect of PIEB according to the flow rate (100 mL/hour vs 300 mL/hour), reported that hourly consumption of epidural analgesics was not improved by high flow epidural administration.[6] In line with this, our results showed no difference of epidural analgesic consumption between PIEB and manual injection. There were some differences in the design between our study and Lange's. Since Lange et al. conducted the study using only the PIEB machine,[6] the difference in infusion pressure between groups might not be significant. Considering that the analgesic consumption may be related to the provided flow rate of epidural analgesics, we provided higher infusion flow rate (1200 mL/hour) by manual injection. In addition, the flow rate of the PIEB group was selected as the maximum value that can be set in the machine we used (240 mL/
As a result, the flow rate in PIEB group was sufficient to provide effective labor analgesia compared to the high flow of manual group. In Lange’s study, the authors suggested that several factors may affect these results, including the size of epidural catheter and the number of orifices, the dose and concentration of local anesthetic, and infusion rate of the bolus drug. To exclude the influence of external circumstances, we equally applied epidural analgesics, type of epidural catheter, and PCEA machine to each group in this study. Consequently, we suggest that the flow rate of epidural bolus injection for adequate labor analgesia does not need to be excessively high. It will be possible to provide effective labor analgesia within the range of the flow rate provided by the machine.

PIEB has superior analgesic effect than continuous infusion because drugs are distributed at high pressure in epidural space and effectively blocking the sensory nerves blockade. Since most PCEA machines allowed the limit of high rates as 200-300 ml/hour, it is insufficient to assess the effectiveness of high-flow versus low-flow epidural infusion. We expected that manual infusion would increase the diffusion range by promoting the drug to flow better within the epidural space. However, our findings showed that the labor analgesia effect of manual injection was not different from that of PIEB. Although this study has not established which flow rate range can provide optimal labor analgesic effects, we found that the infusion flow rate into the epidural space does not need to be as high as manual infusion. Therefore, it is expected that parous women will obtain sufficient analgesic effect by using the PIEB machine.

Intermittent boluses were associated with a greater surface area of diffusion than continuous infusion.[16] Thus, local anesthetics do not stay in a specific epidural space for a long time and are distributed in a large space at a fast rate in PIEB. On the contrary, since the concentration of local anesthetics easily elevates in the extraneural space than intraneural space in continuous infusion, motor blockade frequently occurs.[3, 17] Preserving the motor function during labor analgesia maintains the pelvic muscle tone. It enables smooth pushing during the delivery process and reducing
the transition to instrumental delivery. Numerous studies have compared motor blockade according
to the epidural injection method, but the results are not consistent. Capogna et al. showed that the
incidence of motor blockade was low in PIEB than continuous infusion.[18] Inconsistent with this,
there was no difference in the degree of motor blockade between PIEB and continuous infusion in
this study. This discrepancy may be related to the type of local anesthetics. Capogna et al. used 0.125%
levobupivacaine, and we used 0.12% ropivacaine as an epidural analgesic solution. It has been
reported that ropivacaine showed less motor blockade than levobupivacaine in major orthopedic
surgeries under epidural anesthesia.[19] In addition, previous studies using similar concentrations of
ropivacaine as ours did not show a difference in the incidence of motor blockade between continuous
epidural analgesia and PIEB.[8, 11, 20] These evidences support the involvement of the type and
concentration of local anesthetic in the incidence of motor blockade. When selecting the labor
analgesic regimen using epidural analgesia, it would be desirable to apply it to clinical practice
considering that the use of a low concentration and large volume of local anesthetic promotes effective
labor analgesia without motor blockade.[21]

As mentioned above, there was no difference in the incidence of motor blockade regardless of the
method of epidural infusion of local anesthetic in this study. However, the conversion rate to Cesarean
section was significantly lower in the PIEB group. Our results contradict the study of Huang et al.
that reported no difference between PIEB and continuous infusion in the conversion rate of mode of
delivery.[22] In particular, there was no difference in the mode of delivery conversion rate according
to the epidural infusion method in studies using the same local anesthetic at a concentration similar
to this study.[8, 11, 23] Since we used low concentrations and high doses of local anesthetic in this
study, local anesthetic could have been more effectively distributed in the epidural space in PIEB
group than in the other groups. In contrast, a higher dose of local anesthetic could have been
distributed in the extraneural space in continuous infusion group. A previous meta-analysis

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investigating the rate of assistant vaginal delivery according to the concentration of local anesthetics (high vs low concentration) supported our suggestion.[24]

We acknowledged several limitations in this study. First, we use the CSE method rather than the simple epidural analgesia as the labor analgesia method and the same intrathecal agent was administered to all participants. Thus, the outcomes in our study may have been affected by the extension of the duration and range of intrathecal drugs. However, the duration of intrathecal ropivacaine is less than 100 min.[25] Considering that all groups in our study applied PCEA more than 390 minutes, it is expected that the effects of intrathecal agents disappeared when our secondary outcome was measured. Second, depending on the specifications of the PCEA machine used in each institute, different results may be obtained. In addition, each local anesthetics using for labor analgesia have different viscosity.[26] Future studies are needed on the effect of different PCEA machines and local anesthetics on the flow rate and infusion pressure generated when the local anesthetic is distributed into the epidural space. Lastly, the infusion flow rate might not be constant in the manual group. Epidural space is a kind of potential space where the pressure and volume of injected medication can affect to the distribution of the agents. Therefore, there may be individual differences in the pressure generated by the infusion of epidural agents, which have influenced the outcome of the study. However, these effects are problems that can occur not only in the manual group but also in the other two groups. Considering the design of this study as a randomized trial, the influence of epidural space is thought to be evenly distributed in all participants.

In conclusion, PIEB with ropivacaine was superior to continuous epidural infusion in labor analgesia but did not require the high flow provided by manual infusion. Future research is warranted to find the most ideal flow rate for PIEB.
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Table 1. Participants' characteristics

<table>
<thead>
<tr>
<th></th>
<th>Continuous (n = 28)</th>
<th>PIEB (n = 29)</th>
<th>Manual (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>34 (32.36)</td>
<td>33 (30.35)</td>
<td>32 (28.36)</td>
<td>0.108</td>
</tr>
<tr>
<td>Height, cm</td>
<td>163 (160,166)</td>
<td>163 (160,168)</td>
<td>161 (157,165)</td>
<td>0.133</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69 (65,76)</td>
<td>67 (64,72)</td>
<td>68 (62,77)</td>
<td>0.444</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>26.4 (26.9,28.3)</td>
<td>25.4</td>
<td>26.0</td>
<td>0.407</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>39.6 (38.6,40.2)</td>
<td>39.3</td>
<td>39.3</td>
<td>0.580</td>
</tr>
<tr>
<td>ASA PS, 1</td>
<td>28 (100%)</td>
<td>28 (96.6%)</td>
<td>28 (100%)</td>
<td>0.604</td>
</tr>
<tr>
<td>Pre-labor analgesia data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dilation, cm</td>
<td>3 (3,3)</td>
<td>3 (3,3)</td>
<td>3 (3,3)</td>
<td>0.795</td>
</tr>
<tr>
<td>Use of oxytocin</td>
<td>28 (100%)</td>
<td>29 (100%)</td>
<td>28 (100%)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>120 (110, 128)</td>
<td>114 (104, 129)</td>
<td>117 (108, 130)</td>
<td>0.542</td>
</tr>
<tr>
<td>diastolic blood pressure, mmHg</td>
<td>68 (62, 78)</td>
<td>70 (64, 78)</td>
<td>67 (64, 70)</td>
<td>0.796</td>
</tr>
<tr>
<td>Mean blood pressure, mmHg</td>
<td>87 (78, 95)</td>
<td>85 (79, 96)</td>
<td>86 (80, 87)</td>
<td>0.860</td>
</tr>
<tr>
<td>Heart rate, beats each minute</td>
<td>65 (61, 75)</td>
<td>64 (60, 72)</td>
<td>71 (63, 80)</td>
<td>0.137</td>
</tr>
<tr>
<td>NRS score</td>
<td>6 (5, 8)</td>
<td>6 (5, 7)</td>
<td>5 (5, 6)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Data were expressed as median (interquartile range) and deviation and number (%).

PIEB: programmed intermittent epidural bolus; BMI, body mass index;
ASA PS, American Society of Anesthesiologists Physical Status; NRS, numerical rating scale
<table>
<thead>
<tr>
<th>Table 2. Labor analgesia related variables</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td><strong>Continuous (n = 28)</strong></td>
</tr>
<tr>
<td><strong>PIEB (n = 29)</strong></td>
</tr>
<tr>
<td><strong>Manual (n = 28)</strong></td>
</tr>
<tr>
<td><strong>P value</strong></td>
</tr>
<tr>
<td><strong>PCEA usage</strong></td>
</tr>
<tr>
<td><em>Total consumption, mL</em></td>
</tr>
<tr>
<td>109 (77, 136)</td>
</tr>
<tr>
<td>75 (50, 95)</td>
</tr>
<tr>
<td>73 (55,100)</td>
</tr>
<tr>
<td><strong>0.003ab</strong></td>
</tr>
<tr>
<td><em>Duration of application, min</em></td>
</tr>
<tr>
<td>417 (294,489)</td>
</tr>
<tr>
<td>488 (308,775)</td>
</tr>
<tr>
<td>442 (328,665)</td>
</tr>
<tr>
<td>0.285</td>
</tr>
<tr>
<td><strong>Breakthrough pain</strong></td>
</tr>
<tr>
<td><em>Incidence, %</em></td>
</tr>
<tr>
<td>22 (78.9%)</td>
</tr>
<tr>
<td>19 (65.5%)</td>
</tr>
<tr>
<td>14 (50.0%)</td>
</tr>
<tr>
<td>0.081</td>
</tr>
<tr>
<td><em>NRS score</em></td>
</tr>
<tr>
<td>4.0 (3.8, 4.0)</td>
</tr>
<tr>
<td>4.0 (3.0, 4.0)</td>
</tr>
<tr>
<td>3.5 (3.0, 4.0)</td>
</tr>
<tr>
<td>0.195</td>
</tr>
<tr>
<td><em>Time to express the breakthrough pain, min</em></td>
</tr>
<tr>
<td>78.5 (35.8, 185.0)</td>
</tr>
<tr>
<td>200.0 (88.5, 441.5)</td>
</tr>
<tr>
<td>60.5 (37.3,162.0)</td>
</tr>
<tr>
<td><strong>0.027ab</strong></td>
</tr>
<tr>
<td><strong>Four hours after labor analgesia</strong></td>
</tr>
<tr>
<td><em>Sensory blockade</em></td>
</tr>
<tr>
<td>T7 (5, 8)</td>
</tr>
<tr>
<td>T7 (5, 9)</td>
</tr>
<tr>
<td>T7 (6, 8)</td>
</tr>
<tr>
<td>0.974</td>
</tr>
<tr>
<td><em>Motor blockade+</em></td>
</tr>
<tr>
<td>6 (6, 6)</td>
</tr>
<tr>
<td>6 (6, 6)</td>
</tr>
<tr>
<td>6 (6, 6)</td>
</tr>
<tr>
<td>0.224</td>
</tr>
<tr>
<td><em>NRS score</em></td>
</tr>
<tr>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>0.066</td>
</tr>
</tbody>
</table>

Data were expressed as median (interquartile range) and frequency (%).

PIEB: programmed intermittent epidural bolus, PCEA: patients controlled epidural analgesia, NRS: numerical rating scale score

+ the degree of motor blockade was graded using the Breen-modified Bromage score (1= complete block, unable to move feet or knees; 2= almost complete block, only able to move feet; 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= being able to stand and perform a partial knee bend).

a $P < 0.05$, continuous vs PIEB

b $P < 0.05$, continuous vs manual
Figure 1. CONSORT diagram

PIEB, programmed intermittent bolus infusion
Figure 2. The hourly consumption of epidural analgesics

Box-and-whisker plots (Tukey) indicated the median (interquartile range) with max and min values.

Dots indicated outliers.

PCEA: patient controlled epidural analgesia, PIEB: programmed intermittent epidural bolus