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ORIGINAL RESEARCH

Programmed Intermittent Epidural Bolus in Comparison with Continuous Epidural Infusion for Uterine Contraction Pain Relief After Cesarean Section: A Randomized, Double-Blind Clinical Trial

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Purpose: Programmed intermittent epidural bolus (PIEB) was reported to provide superior maintenance of labour analgesia with better pain relief and less motor block than continuous epidural infusion (CEI). Whether this is also evident for uterine contraction pain relief after cesarean section remains unknown.

Patients and Methods: Parturients scheduled for cesarean section were recruited for the study. At the end of the surgery, after a similar epidural loading dose given, patients received either PIEB (6 $mL{\cdot}h^{-1}$) or CEI (6 $mL{\cdot}h^{-1}$) of 0.1% ropivacaine. The primary outcome was the uterine contraction pain assessed with visual analog scale (VAS-U) at the postoperative 36 h. Secondary outcomes included incision pain at the rest (VAS-R) and in the movement-evoked (VAS-P), and lower extremity motor block (defined as Bromage score > 0). The whole profile of VAS scores between groups was analyzed using linear mixed model. When significant differences were found, the pairwise comparison was done with the Mann Whitney *U*-test followed by Bonferroni correction.

Results: One hundred and twenty parturients were studied (PIEB, 60; CEI, 60). VAS-U at the postoperative 36 h in the PIEB group was lower than in the CEI group (Bonferroni-adjusted $P < 0.01$). The linear mixed model indicated that VAS-U, VAS-R and VAS-P were lower in the PIEB group compared with the CEI group (all $P < 0.01$). Motor block was higher in the CEI group than in the PIEB group during the study period except 2 h (all $P < 0.05$). No differences of adverse events such as hypotension and urinary retention were observed between the two groups.

Conclusion: Programmed intermittent epidural bolus provides more effective uterine contraction and incision pain relief and less motor block after cesarean section than continuous epidural infusion without an increased risk of urinary retention and blood pressure instability.

Keywords: cesarean section, epidural, pain, postoperative analgesia, uterine contraction

Introduction

Women often experience uterine contraction pain after cesarean section. This type of pain results in extensive neuroendocrine stress responses[1,2] and inadequate analgesia increased the risk of breastfeeding failure,[3] impaired maternal-infant interaction,[3] chronic pain[4] and postpartum depression,[5] and postoperative morbidities and negated quality of life.[6]

Multimodal analgesia approach with intrathecal opioids, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) greatly improved pain control for the majority of patients after cesarean section.[7] However, there remains a proportion of women for whose postoperative pain relief and patient satisfaction are still inadequate,[8] and some women

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are concerned about the potential negative effects of these drugs during breastfeeding.[9,10] Compared with systemic administration (such as intravenous, intramuscular and oral) of analgesics, epidural administration of local anesthetics transferred into breast milk was minimal and thus epidural analgesia was considered to be safely used for postpartum analgesia.[10,11]

Previous meta-analysis[12,13] showed that epidural analgesia provided significantly superior analgesia compared with patient-controlled intravenous analgesia and parenteral opioids. Several studies[14–16] demonstrated that epidural analgesia was safely and effectively used for post-cesarean section analgesia. Painful impulses caused by uterine contractions are transmitted via visceral afferent nerve fibers which accompany sympathetic nerve fibers and enter into the spinal cord at the T10-L1 spinal segments.[17] If most of these pathways can be successfully blocked by epidural analgesia, uterine contractions pain would be alleviated.

Programmed intermittent epidural boluses (PIEB), a newly established technology, provides better analgesia, less motor block and lower local anesthetic drug consumption compared with traditional continuous epidural infusion (CEI), which has being used in labour analgesia.[18–21] Therefore, we hypothesized that PIEB may provide superior uterine contraction pain and incision pain relief and less motor block than CEI. Our primary aim was to evaluate the effectiveness of uterine contraction pain relief assessed with visual analog scale (VAS) score at the postoperative 36 h.

Materials and Methods

Study Design and Participants

Patient inclusion criteria were ASA Physical Status 2 or 3, aged 18 to 45 years, term gestation (≥ 37 weeks), singleton pregnancy, parity 0 or 1, scheduled for elective cesarean section under combined spinal-epidural anesthesia, planned on breastfeeding. Exclusion criteria were contraindications to neuraxial anaesthesia, BMI ≥ 40 $kg \cdot m^{-2}$, severe pregnancy complications, use of sedative or analgesic drugs 2 h before surgery, allergy to drugs used in the study, or known fetal abnormalities.

Ethics

The trial was registered prior to patient enrolment at chictr.org.cn (ChiCTR2000032645). The study protocol was approved by the local ethics committee, the Guangzhou Women and Children's Medical Centre Ethics Committee, Guangzhou, China on 27 May, 2020 (The reference number 2020-27601). This trial adheres to the Consolidated Standards of Reporting Trials guidelines and complies with Declaration of Helsinki. All participants gave written informed consent prior to study commencement. The trial was carried out from 31 May 2020 to 11 October 2020.

Randomization and Blinding

Consenting parturients were randomly assigned to the PIEB group or the CEI group using a computer-generated randomization list (in a 1:1 ratio). The intensity of uterine contraction pain increased with parity, so to avoid imbalances due to parity, randomization was stratified by parity 0 or 1 in a 1:2 ratio (nulliparous parturients, 40; multiparous parturients, 80). Two sets of random numbers (40 and 80, respectively) were generated by computer and allocation was concealed by sequentially numbered sealed opaque black and white envelopes, respectively. Patients of nulliparous parturients were assigned into the PEIB or CEI group according to random numbers in black envelopes while patients of multiparous parturients were assigned into the PEIB or CEI group according to random numbers in white envelopes. A staff who did not participate in the study organized and kept randomization code until study completion. Patients, anaesthesia providers, obstetricians and researchers were blind to the group assignments.

Anaesthesia, Surgery, and Postoperative Analgesia

After an intravenous catheter was placed, and the patient was transported to the operating room, where standard ASA monitors were placed and a fluid co-load with Lactated Ringer's was started. With the patient in a left lateral decubitus position, a 25-gauge pencil-point needle was introduced into the subarachnoid space at the L3-L4 or L2-L3 interspace in a standard sterile fashion. After return of clear cerebrospinal fluid, 12–15 mg of 0.5% ropivacaine which was diluted by

cerebrospinal fluid was administered. Then a single-orifice epidural catheter was placed 4 cm into the epidural space and a 3 mL epidural test dose of 1% lidocaine was administered. After immediately positioned supine with a 15° left lateral tilt, pinprick test was done to ensure that sensory block was above T6. If sensory block was not achieved to the T6 level, or the patient experienced intraoperative pain, 2% lidocaine was administered into the epidural space to achieve adequate anaesthesia. All subjects received a prophylactic intravenous phenylephrine infusion initiated at 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at the time of spinal injection.

After delivery of the baby, oxytocin was administered as per hospital protocol and each patient received 12.5 mg dolasetron intraoperatively for vomiting prophylaxis. At the end of the surgery, the same solution of loading dose contained 0.125% ropivacaine 8 mL with hydromorphone 0.6 mg and naloxone 0.04 mg was administered in two groups via the epidural catheter and group assignments were opened by an anesthesia research nurse. Epidural analgesia was maintained with a solution of 0.1% ropivacaine alone. In the PIEB group, the epidural pump (Apon MC ZZB—IV; Jiangsu Apon Medical Technology, Jiangsu, China) was programmed to deliver a 6-mL bolus at a rate of 360 $mL \cdot h^{-1}$ every hour beginning 30 minutes after administration of the loading dose. In the CEI group, the pump (Apon ZZB—I; Jiangsu Apon Medical Technology, Jiangsu, China) was programmed to deliver at a constant rate of 6 $mL \cdot h^{-1}$ immediately after the loading dose. Both pump settings were set with a patient-controlled epidural analgesia (PCEA) of 6 mL with a lockout interval of 15 min and a maximum hourly volume of 24 mL. The pumps were programmed by an anesthesiologist not involved in data collection and inserted into an opaque, portable bag to maintain blinding. Before leaving the operating room, patients were instructed to use PCEA with a standardized instruction whenever she felt uncomfortable. If the parturient still felt pain after activating the PCEA bolus twice in a 30-min period, rescue analgesia with 100 mg rectal diclofenac potassium suppository was allowed as a rescue option.

Peri-operative monitoring consisted of hourly respiratory rate, pulse rate and non-invasive blood pressure measurements for 6 h and thereafter at intervals of 8 h by nursing staff. In the obstetrical ward, 10 units oxytocin was intravenously administered for three times at 12-hour intervals after surgery. All other treatments were followed a routine clinical practice including in case of hypotension (defined as systolic blood pressure 20% less than the baseline value or less than 90 mmHg), it was treated with intravenous phenylephrine (20–40 μg) as necessary. Baseline blood pressure was defined as the usual blood pressure at home. The definition of urinary retention was, lack of spontaneous micturition 6 h after the removal of catheter after cesarean section, requiring catheterization.[22]

Pain Evaluation

All data were collected by research team members blinded to the groups at the postoperative 2, 6, 12, 24 and 36 h. The VAS score was used to assess uterine contractile pain and incision pain after cesarean section as reported previously.[2] It is presented as a 100-mm horizontal line (0, no pain; 100 mm, worst imaginable pain). Breastfeeding and oxytocin administration stimulates the uterine contraction and increases the severity of the pains.[23,24] Therefore, the highest VAS score of uterine contractions pain evoked with breastfeeding or oxytocin administration experienced over the designated time interval was defined as the VAS-U. The incision pain at the rest (VAS-R) and in the movement-evoked mainly by changing position in bed (VAS-P) was also evaluated. Uterine contraction pain was defined as an intermittent, indefinite location, short-lasting, while the incision pain was defined as a constant, definite location and evoked abdominal pain over the wound and adjacent region. At the postoperative 36 h, the parturient was also asked to report an overall postpartum experience satisfaction using VAS score (0, completely dissatisfied; 100 mm, completely satisfied).

Outcomes

Primary Outcome

The primary outcome was the VAS-U at the postoperative 36 h.

Secondary outcomes

The key secondary outcomes included VAS-R and VAS-P during the study period, and VAS-U at 2, 6, 12, 24 h, and lower extremity motor block (defined as Bromage score > 0). The degree of motor block was assessed in both lower extremity using a modified Bromage score [0 = no motor paralysis; 1 = unable to raise the extended leg, but able to move

knee and foot; 2 = unable to raise the extended leg as well as flex knees, able to move foot; 3 = not able to flex ankle, foot or knee (complete block)].[25] If the Bromage score of both lower limbs was inconsistent, the higher score was taken. Other secondary outcomes included the PCEA boluses, time to first PCEA bolus, proportion of patients requiring diclofenac potassium suppository rescue. The presence of vomiting, pruritus, hypotension, or urinary retention was recorded throughout the study period as yes or no.

Sample Size Calculation

The sample size estimation was based on the primary outcome. Data from a pilot study including 20 patients suggested that the mean ± standard deviation (SD) VAS-U score at the postoperative 36 h was 30.3 ± 12.8 mm in the PIEB group and 40.2 ± 16.3 mm in the CEI group. A sample size of 48 subjects per group had 90% power at $\alpha = 0.05$ in a 2-sided 2-sample *t*-test to identify this difference calculated using PASS software (version 11. NCSS, LLC. Kaysville, Utah, USA). To take dropouts into account, 120 subjects was planned to be recruited.

Statistical Analysis

Statistical analysis were performed using SPSS (version 25.0, IBM Corp., Armonk, NY, USA). Data were expressed as the mean ± SD, the median (interquartile range, IQR), or the number (proportion) as appropriate. For the normality test, the Kolmogorov–Smirnov test was performed. The differences between groups were compared using the Student's *t*-test (normally distributed data) or Mann Whitney *U*-test (skewed data). Categorical and proportions were analyzed using the Pearson Chi-square test or Fisher exact test as appropriate. The whole profile of VAS scores were assessed between groups with linear mixed model. The models consisted of main effects for treatment group and time. The test was followed the Mann Whitney *U*-test with Bonferroni adjustment for multiple pairwise comparisons (5 comparisons) if a significant intergroup difference was found. A Bonferroni-adjusted *P* value <0.01 (0.05/5) was considered statistically significant. Time to first PCEA bolus was analyzed by using the Kaplan Meier curves with a Log rank test. An intention-to-treat analysis was performed with a *P* value < 0.05 considered to be of statistically significant.

Results

Participants

A total of 133 patients were assessed for eligibility. After exclusion, 120 participants were included and randomized to either the PIEB group or the CEI group (Figure 1). Baseline characteristics are presented in Table 1.

Pain Scores

The linear mixed model showed a significant main effect of group and a significant effect of time and a significant group-by-time interaction in VAS-U, VAS-R and VAS-P. Three types of pain VAS scores were all significantly lower in the PIEB group compared with the CEI group (For VAS-U, $P = 0.001$; For VAS-R, $P < 0.001$; For VAS-P, $P = 0.008$). Three types of pain levels were increased over time in both groups (all $P < 0.001$) (Figure 2). The group-by-time interaction was significant (all $P < 0.05$), indicating that the PIEB group had significantly lower three types of pain VAS scores over time than the CEI group. The primary outcome, VAS-U at the postoperative 36 h, was significantly lower in the PIEB group [median (IQR), 30 (20 to 40) mm] compared with the CEI group [40 (30 to 50) mm], with an estimated difference of −10 mm (95% CI −15 to −5 mm; Bonferroni-adjusted $P < 0.01$ after Mann Whitney *U*-test) (Figure 2). The VAS-R scores at the postoperative 12 and 36 h were significantly lower in the PIEB group than in the CEI group (Bonferroni-adjusted $P < 0.01$) (Figure 2). The VAS-P scores at the postoperative 36 h were significantly lower in the PIEB group than in the CEI group (Bonferroni-adjusted $P < 0.01$) (Figure 2).

Motor Block

Motor block occurred more frequent in the CEI group compared with the PIEB group at the postoperative 6 h (40% vs 16.7%; $P = 0.005$), 12 h (25% vs 3.3%; $P = 0.001$), 24 h (15% vs 1.7%; $P = 0.008$) and 36 h (10% vs 0%; $P = 0.003$) (Figure 3).

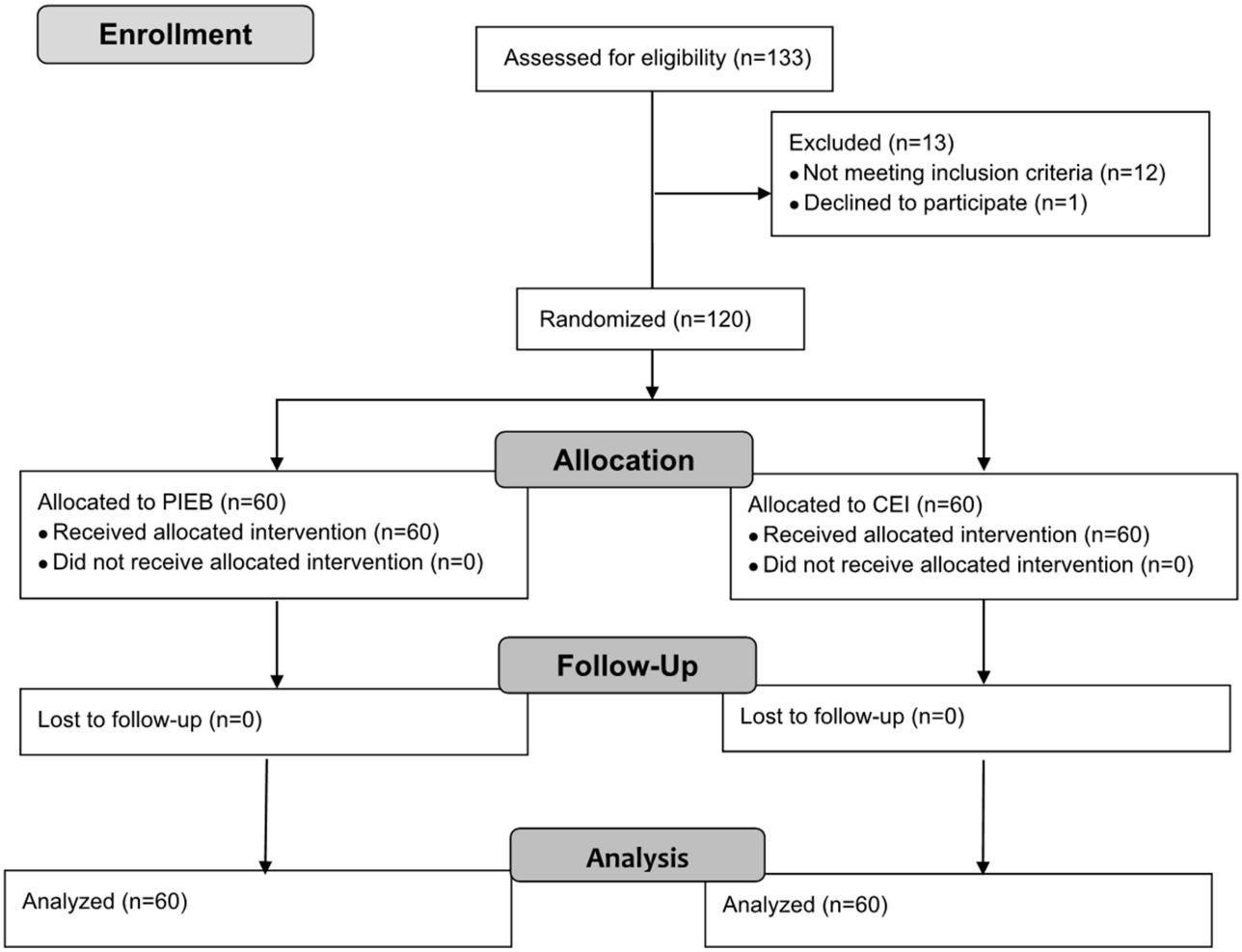

Figure 1 Flowchart of the study.
Abbreviations: CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus.

PCEA Administrations, Rescue Analgesia Usages and Patient Satisfaction

The number of PCEA boluses was less in the PIEB group than that of the CEI group [median (IQR), 1 (0 to 5) vs 3 (1 to 10); $P = 0.02$]. The PIEB group had a longer median time to first PCEA (22 h; 95% CI, 10–28 h vs 16 h; 95% CI, 11–24 h; $P = 0.016$; Figure 4) compared with the CEI group. The percentage of patients who received diclofenac potassium suppository rescue was 27.8% in the PIEB group and 30.0% in the CEI group ($P = 0.800$). Maternal satisfaction with

Table 1 Patient Characteristics

Parameters	PIEB Group (n = 60)	CEI Group (n = 60)	*P* value
Maternal age (yr)	33 ± 5	33 ± 5	0.895
Body mass index ($kg \cdot m^{-2}$)	26 ± 3	26 ± 3	0.184
Gestational age (weeks)	38 (38 to 39)	38 (38 to 39)	0.367
ASA physical status			
II	17	11	
III	43	49	0.195
Duration of surgery (min)	45 (35 to 54)	45 (38 to 53)	0.931

Notes: Data are presented as mean ± standard deviation, median (interquartile range), or number. Data were analyzed using the Student's *t*-test, Mann Whitney *U*-test, or Pearson Chi-square test.
Abbreviations: CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus.

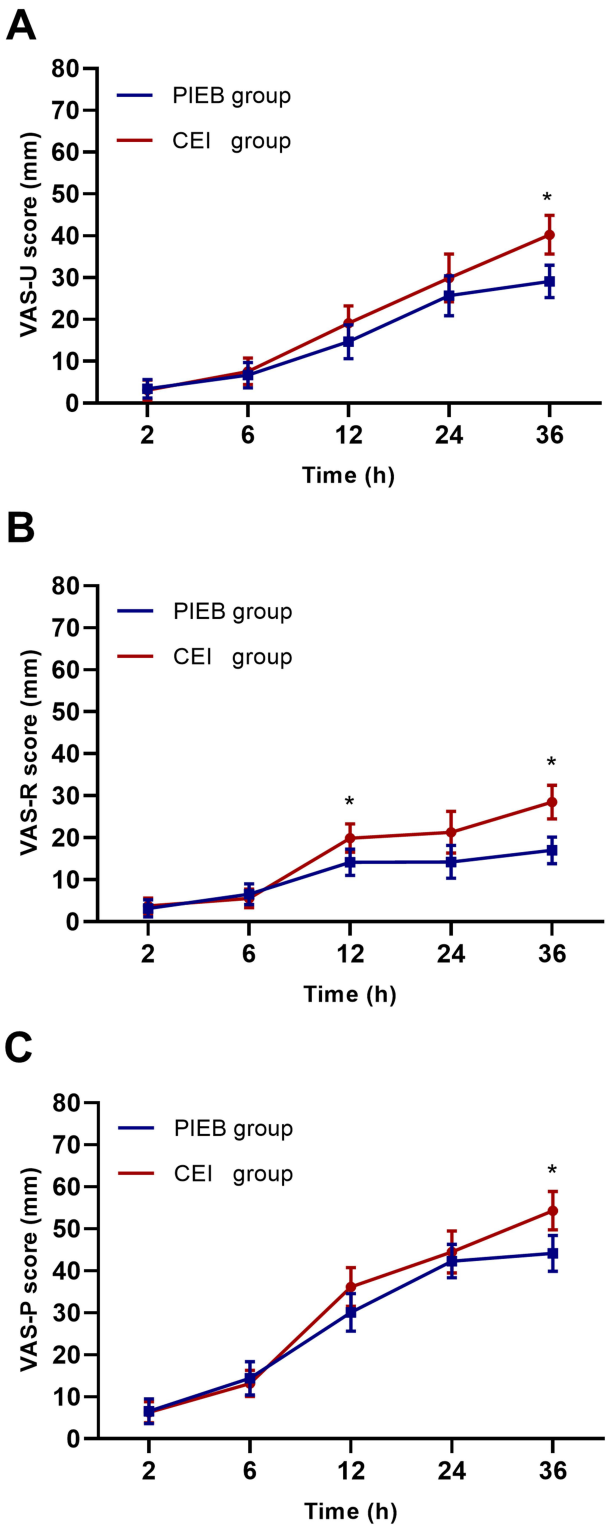

Figure 2 The mean changes in VAS-U (**A**), VAS-R (**B**) and VAS-P (**C**) in PIEB and CEI group patients over time after cesarean section. Error bars represent 95% CI of the mean. Three types of pain levels were increased over time in both groups using the linear mixed model (all $P < 0.001$). *Bonferroni-adjusted $P < 0.01$ after Mann Whitney *U*-test between the two groups. A, A linear mixed model showed that VAS-U scores were significantly lower in the PIEB group compared with the CEI group ($P = 0.001$), which indicates a significant difference between groups with a significant overall treatment effect. B, Similarly, VAS-R scores were significantly lower in the PIEB group compared with the CEI group ($P < 0.001$). C, VAS-P scores were significantly lower in the PIEB group compared with the CEI group ($P = 0.008$).

Abbreviations: CEI, continuous epidural infusion; CI, confidence interval; PIEB, programmed intermittent epidural bolus; VAS-U, VAS-R, VAS-P, visual analog scales for uterine contractions pain, for incision pain at the rest and in the movement-evoked mainly by changing position in bed, respectively.

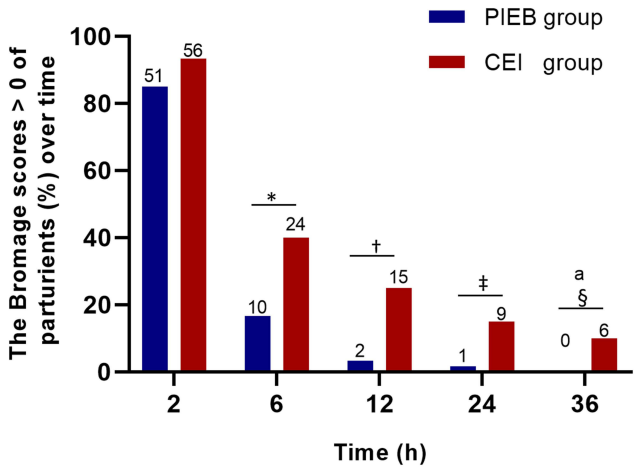

Figure 3 The percentage of parturients with the Bromage score > 0 of lower extremity over time.
Notes: Data were analyzed using the Pearson Chi-square test or Fisher exact test as appropriate. *P = 0.005, †P = 0.001, ‡P = 0.008, §P = 0.003 the PIEB vs CEI group at the corresponding time point. [a]Fisher exact test used.
Abbreviations: CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus.

overall postpartum experience was greater in the PIEB group than in the CEI group [median (IQR), 88 (80 to 90) vs 80 (70 to 90); P = 0.004].

Side Effects

Complications are shown in Table 2. The incidence of vomiting, pruritus, hypotension, or urinary retention did not differ between the two groups.

Discussion

This randomized, double-blind clinical trial demonstrated that PIEB provided more effective uterine contraction and incision pain relief in patients after cesarean section compared with CEI. In addition, PIEB was associated with reduced incidence of motor block, less PCEA boluses, longer time to first PCEA bolus, and higher patient satisfaction without an increased risk of hypotension and urinary retention in patients after cesarean section when compared with CEI.

In recent years, PIEB becomes popular with the anesthesiologist and parturients for vaginal birth pain relief because PIEB has demonstrated superiority to CEI for providing better pain relief, reduced motor block, and improved patient

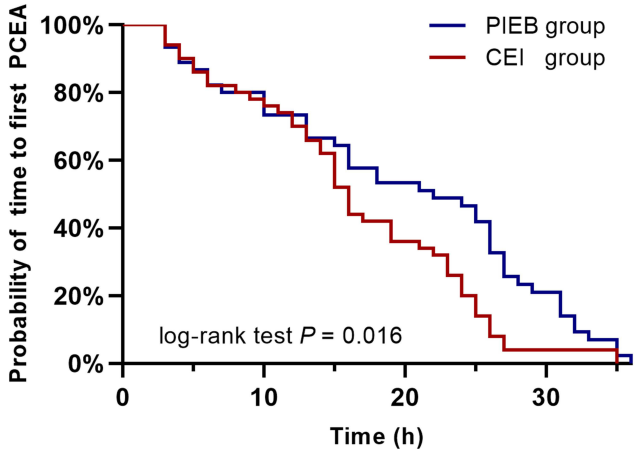

Figure 4 The time to first PCEA analyzed and presented with Kaplan-Meier Survival Curves.
Note: Event rates were based on Kaplan-Meier estimation of the time-to-first-event analysis.
Abbreviations: CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus; PCEA, patient-controlled epidural analgesia.

Table 2 Complications: Vomiting, Pruritus, Hypotension and Urinary Retention

Parameters	PIEB Group (n = 60)	CEI Group (n = 60)	*P* value
Vomiting, n (%)	16 (26.7%)	14 (23.3%)	0.673
Pruritus, n (%)	45 (75.0%)	42 (70.0%)	0.540
Hypotension, n (%)	0	0	–
Urinary retention, n (%)	1 (1.7%)	1 (1.7%)	1

Notes: Data are presented as number (proportion). Data were analyzed using Pearson Chi-square test, or Fisher exact test as appropriate.
Abbreviations: CEI, continuous epidural infusion; PIEB, programmed intermittent epidural bolus.

satisfaction,[21,25–29] which is consistent with our findings that PIEB provided more effective post-cesarean uterine contraction pain relief and less motor block. Recently, PIEB was reported to be used for incision pain management in surgical patients in previous studies.[30–33] We also found that PIEB provided more effective post-cesarean incision pain relief. These findings were similar to the findings reported by previously.[33] In contrast, Su et al[30] found that the average pain severity after major abdominal surgery was not different between PIEB and CEI groups. This was likely due to that all subjects received a postoperative multimodal analgesic regimen, which might mask the advantages of PIEB.

Our study demonstrated that the peak pain level of incision pain evoked by movement and at the rest, and uterine contraction pain were at 36 h after cesarean section in the both groups, which is consistent with the findings reported previously.[2] The reasons may be as follows: First, the sensory blockade of ropivacaine for spinal anaesthesia lasted approximately 200 min,[34] and a single-dose epidural hydromorphone also extended its effects for up to up to 24 h.[35–37] These results may suggest that postoperative analgesia regimen should be applied to patients during the whole hospitalization, especially the second day after cesarean section.

An in vitro study demonstrated that intermittent bolus of the epidural catheter has a wider spread of methylene blue dye solution compared with continuous infusion.[38] In a porcine model, the mean longitudinal extent spread of 1 mL dye administration was 8.9 ± 2.6 cm in the continuous infusion group compared with 15.2 ± 2.7 cm in the bolus group.[39] In another porcine model study, the spread of epidural radiopaque contrast dye was 5.6 vertebral levels in the continuous infusion group compared with 10.4 in the bolus group.[40] Furthermore, a clinical study comparing epidural bolus and CEI administration after abdominal surgery showed that the median number of blocked spinal segments was 19.5 in the epidural bolus group and 11.5 in the CEI group, indicating that epidural bolus administration provided greater longitudinal extension of sensory blockade than CEI.[41] Therefore, it is very likely that PIEB providing more effective uterine contraction pain and incision pain relief after cesarean section than CEI was due to that the PIEB blocked the sensory-nerve fibers more extensively.

A randomized study of labour analgesia showed that the incidence of motor block was 2.7% in parturients administered PIEB and 37% in those received CEI,[29] which is comparable to these of our study at 12 h (3.3% in the PIEB group vs 25% in the CEI group). Two meta-analysis[19,21] of labour analgesia also demonstrated that PIEB produced less motor block compared with CEI. Analgesia and motor block are produced by the movement of local anaesthetic from the extraneural space into the intraneural space along a diffusion gradient. If low concentrations of local anaesthetic are given in CEI, the concentration of local anaesthetic in the extraneural is persistently higher than in the intraneural space, which increases the concentration in the nerve and reaches the threshold for motor fiber block.[42] However, in the case of PIEB, blockade of motor fibers is less because the total amount of local anaesthetic in the nerve is insufficient.[42] The advantage of PIEB in reducing motor block suggests that it allows early mobilization to enable these women to care for their newborn and facilitates early discharge from hospital. The overall satisfaction of mothers was higher in PIEB group than in the CEI group, which may be due to the lower pain score and less motor block in the PIEB group.

While improving the analgesic effect, one may be concerned about the increased risk of hypotension and urinary retention. Our study found no hypotension requiring treatment in both groups, and urinary retention did not differ between groups. However, Wei et al[32] compared continuous infusion with intermittent bolus for postoperative analgesia in patients after thoracic surgery, reported the incidence of hypotension was 18.5% in the intermittent group and 53.6% in the continuous group. Two possible explanations for the discrepancy between our study and Wei's study are that the

epidural catheter was placed in T7-T8 interspace in their study, which may lead to cardiac sympathetic block, and they used a higher local anaesthetic concentration (0.3% ropivacaine) than our study.

Our study also has limitations. First, although the study was designed to be double-blinded, it is possible that patients and investigators might have been aware of grouping by the different sounds of pump injection. Second, although continuous postpartum epidural analgesia is not a common analgesic model clinically, this study may provide a reference for PIEB as the part of a multimodal analgesia regimen. In addition, if PIEB combined with NSAIDS and opioids, it may reduce the dosage and side effects of each other.

Conclusion

In conclusion, we found that the maintenance of epidural analgesia with PIEB provided better uterine contraction and incision pain relief, less motor block, fewer PCEA boluses, longer time to first PCEA bolus, and higher patient satisfaction without an increased risk of hypotension and urinary retention in patients after cesarean section when compared with CEI.

Data Sharing Statement

The data collected for this study can be shared with researchers in de-identified form after the publication date, and in the presence of a data transfer agreement, and if it complies with China legislation. Requests for data and study proposal should be directed to sxjess@163.com, including a proposal that must be approved by the trial's steering committee.

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Disclosure

The authors report no conflicts of interest in this work.

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