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ORIGINAL RESEARCH

Effectiveness of Patient-Controlled Intravenous Analgesia (PCIA) with Sufentanil Background Infusion for Post-Cesarean Analgesia: A Randomized Controlled Trial

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Purpose: To investigate the effectiveness of sufentanil patient-controlled intravenous analgesia pump (PCIA) and background infusion in patients of post-cesarean analgesia.

Patients and Methods: This trial compared two groups of women undergoing cesarean section and receiving PCIA: no background infusion group (n=30), 6-min lockout time, and background infusion group (n=30), 2 mL/h infusion, 10-min lockout time. Both groups with 2 μg/kg sufentanil was diluted to 100 mL with normal saline. VAS scores at rest at 36 h was the primary endpoint. The secondary endpoints were the VAS scores at rest at 6, 12, and 24 h, the total amount of sufentanil consumed, the Ramsay sedation score (RSS) assessed at the same time points, postpartum bleeding within 24 h, the injection/attempt (I/A) ratio, BP and HR, PONV, side effects of sufentanil.

Results: Compared with the no background infusion group, the background infusion group showed lower VAS pain scores at 6, 12, and 24 h ($P<0.01$), but no differences at 36 h (95% CI = −0.5–0.8. $P>0.05$). Attempts, injections, and total sufentanil consumption were significantly different between the two groups ($P<0.001$), but without difference in I/A. Bleeding was less in the background infusion group at 1 h ($P=0.03$). The minimal respiration rates were not significantly different between groups.

Conclusion: Background infusion increased the total consumption of sufentanil within 36 h after cesarean section. Although it did not reduce uterine contraction pain and wound pain at 36 h, it significantly reduced the pain at 6, 12, and 24 h after cesarean section. It improved patient satisfaction and reduced the amount of bleeding after 1 h. Importantly, it did not increase the incidence of hypertension, PONV and respiratory depression.

Keywords: background infusion, patient-controlled intravenous analgesia, PCIA, sufentanil

Introduction

Pain after cesarean section is usually ranked moderate to severe.[1] Management of pain after birth is important and can impact a woman's return to normal activities and caring for her baby and shorten lactogenesis.[2] Traditionally, intravenous administration of opioids has been successfully used for pain control after cesarean section.[3] Patient-controlled intravenous analgesia pump (PCIA) is a commonly used method to relieve postoperative pain in hospitalized patients. The method is to titrate analgesics according to demand. Compared with "on-demand" opioid injections, it usually provides better pain control and improves patient satisfaction.[4,5] The PCIA prescription includes the parameters programmed into the PCIA machine, such as bolus dose, lockout interval, dose limits, and background infusion. Each may have some effect on the safety and efficacy of PCIA.

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A panel of the American Pain Society recommends against routine background infusion of opioids with PCIA in opioid-naïve adults because a background infusion of opioids is associated with an increased risk of nausea and vomiting, and in some studies with increased risk of respiratory depression in adults.[6–10] Still, conflicting results were reported. Indeed, a study showed that adding a background morphine infusion to a standard morphine PCIA improved post-operative analgesia without increasing the side effects.[11]

Sufentanil, one of the opioids with the strongest analgesic potency, is now widely used for anesthesia of surgery patients, and has also been extensively used in postoperative pain control and labor pain relief.[12–14] Furthermore, Grass et al suggested that a small background infusion might be necessary to sustain analgesia with sufentanil.[15] Zhen et al[16] and Gao et al[17] showed that PCIA with background infusion of sufentanil achieved good analgesia without increased adverse effects after abdominal surgery. Similar results were observed for thoracotomy.[18]

This randomized controlled trial (RCT) aimed to investigate the effectiveness of sufentanil PCIA and background infusion in patients of post-cesarean analgesia.

Materials and Methods

Study Design

This study was a prospective, single-blind, randomized controlled trial with a two-arm parallel-group design in the gynecology and obstetrics department of Shanxi Bethune hospital from June 2020 to March 2021.

The inclusion criteria were 1) nulliparous women, 2) aged 18–40 years, 3) planned to undergo a cesarean section, 4) body mass index (BMI) of 18–29 kg/m^2, 5) American Society of Anesthesiologists (ASA) grade I to II, and 6) no smoking history. The preoperative exclusion criteria were 1) severe heart, lung, liver, or kidney insufficiency, 2) hypertension during pregnancy, 3) preoperative fetal distress, 4) history of mental or neurological diseases, 5) opioid allergies, 6) opioid tolerance, 7) smoking history, 8) history of motion sickness, or 9) history of postoperative nausea and vomiting (PONV). The postoperative exclusion criteria were 1) re-operation exploration, 2) hemodynamic instability, including systolic blood pressure (SBP) <90 mmHg, severe arrhythmia, or hemorrhage,[11] or 3) postoperative confusion.

After approval from the ethics committee of Shanxi Bethune Hospital (#YXLL-SL-2020-017), consenting parturients were included in this prospective randomized study. Written informed consent was obtained from all subjects. The study was registered prior to patient enrollment at the Chinese Clinical Trial Register (Register number: ChiCTR2000037940), participating in the World Health Organization International Clinical Trials Registry Platform. The trial was conducted according to the tenets of the Declaration of Helsinki and the Good Clinical Practice.

Randomization and Blinding

A Microsoft Excel "Random" function-generated randomization sheet was used for randomization. The randomized sheet was kept by the qualified clinical research pharmacist who managed the drugs. The participants were blinded to the intervention.

Intervention

All parturients received 500 mL of intravenous Ringer's solution before epidural analgesia. All participants received combined spinal and epidural anesthesia (CSEA) at the L3-4 or L2-3 space using the needle-through-needle technique. A 16–18mg of 0.5% ropivacaine injection was given to subarachnoid space. When the effect of subarachnoid block was poor, 3–5mL of 1.5% lidocaine was added to epidural space. If hypotension occurred (SBP <90 mmHg or a reduction >20% of the basal SBP), 50 μg of phenylephrine was administered intravenously, and fluid infusion was sped up. When the SBP was higher than 180 mmHg, the infusion rate was lowered, and 25 mg of urapidil or 0.1 mg of nicardipine was administered intravenously. If the heart rate (HR) was <50 bpm, 0.2 mg of atropine was intravenously injected. The parturients were sent to the post-anesthesia care units (PACU) after surgery. When vital signs were stable and the sensory block was not higher than T8, the PCIA pumps were connected in the PACU, and then the parturients were sent back to their ward. The PCIA pumps were discontinued after 36 h for all participants.

According to body weight, 2 μg/kg sufentanil (Yichang Humanwell Pharmaceutical Jiangxi Province China) was diluted to 100 mL with normal saline. The 60 parturients had a PCIA analgesia protocol initiated consisting of a 0.5-mL bolus and were then randomized to no background infusion, 6-min lockout time (no background infusion Group), or 2 mL/h infusion, 10-min lockout time (background infusion Group). The drugs were delivered in a sealed opaque envelope before surgery, and the envelope was opened in the operating room only by a non-blinded anesthesiologist who was responsible for anesthesia management and setting the PCIA as per the protocol in the operating room. All other investigators who assessed the study endpoints after the operation in the PACU and the ward were blinded to group assignment. All the PCIA devices were applied to parturients with labels with only the patient's study number so that neither the parturients nor medical care providers and investigators could recognize the PCIA regimen.

The parturients were instructed on using the PCIA pump and told to press the button whenever they felt pain. No other analgesic drug was allowed, but parturients were allowed to receive an intramuscular injection of 100 mg of tramadol when they complained of pain >7 on the VAS; if necessary, the injection could be repeated. Still, analgesia failure had to be excluded. Intravenous metoclopramide 10 mg was given as a rescue antiemetic at the parturients' request. If severe nausea persisted after two consecutive rescue antiemetics, PCIA was stopped for 2 h and restarted later when the symptoms subsided.

Endpoints

Visual analog scale (VAS) scores at 36 h were assessed as the primary endpoint measures. VAS scores included wound pain at rest (VAS-R) scores and uterine cramping pain (VAS-U) scores. The intensity of pain was recorded with a 10-cm VAS, which ranged from 0 (no pain) to 10 (the worst pain imaginable). The secondary endpoints were the VAS scores at 6, 12, 24 h, the total amount of sufentanil consumed, the Ramsay sedation score (RSS)[19] assessed at the same time points, postpartum bleeding within 24 h, the injection/attempt (I/A) ratio, PONV, side effects of sufentanil. The I/A ratio compares the number of actual analgesic doses delivered with the number of requests for analgesic (attempts). Ideally, I/A ratios should be close to 1, indicating that each patient injection corresponds to one attempt for analgesic administration. PONV was rated on a four-point verbal scale (none = no nausea, mild = nausea but no vomiting, moderate = vomiting one attack, severe = vomiting > one attack). All side effects related to sufentanil, including dizziness, pruritus, headache, and constipation, were examined. Respiratory depression was defined by a respiratory rate <10 per min or oxygen saturation <90% for >1 min.[20] The participants were asked about their satisfaction with PCIA during the previous 36 h, using a scale with 0 meaning not satisfied to 5 meaning very satisfied. The participants were assessed by a trained nurse who was blinded to group assignment. HR and blood pressure (BP) were recorded postoperatively at 6, 12, 24, and 36 h.

Baseline demographic data were recorded, including age, height, weight, BMI, operation time, gestation, in-hospital days, and ASA classification.

Sample Size

In order to determine the appropriate dose of sufentanil in PCIA after surgery, the primary endpoint pain level assessed by VAS was analyzed. The expected standard deviation of the means in the general patient population was 6.9 mm,[16,21,22] and the standard deviation of the participants was 20 mm.[23] The significance level was set at 0.05 and the power at 0.8. Sample size assumption was made through the PASS 11 software (NCSS, LLC, Kaysville, Utah, USA). The calculated sample size was 29 in each group. Finally, 30 patients were included in each group.

Statistical Analysis

Statistical analyses were performed using SPSS 20 (IBM, Armonk, NY, USA). The per-protocol (PP) set was used for analysis in this study. Continuous data were shown as means ± standard deviations or mean differences with 95% confidence interval (95% CI). Categorical data were presented as cases and frequency. The Kolmogorov–Smirnov test was performed to test whether the data conformed to a normal distribution. Differences between the two groups were compared using analysis of repeated-measures ANOVA and independent sample *t*-test. P-values <0.05 were considered statistically significant.

Results

Characteristics of the Participants

A total of 73 patients were assessed for eligibility, and seven were excluded for noncompliance with the study protocol. Thus, 66 patients were randomized: 34 in the no background infusion group and 32 in the background infusion group. Four operations were converted to open hysterectomy, and two patients discontinued IV-PCA due to pump malfunction. Finally, 60 parturients were included in the analysis, with 30 in each group (Figure 1). Table 1 shows the baseline demographic and obstetric data. The values of hemodynamic data remained within the normal range throughout the study period.

Primary Outcome

The comparisons of VAS-R and VAS-U at 36 h are presented in Table 2. There were no significant differences in VAS-R and VAS-U at 36 h between the no background infusion and background infusion groups.

Secondary Outcomes

The comparisons of VAS-R and VAS-U at 6, 12, and 24 h are presented in Table 3. VAS-R and VAS-U were different between the two groups, the background infusion group showed lower VAS-R and VAS-U pain scores at 6, 12, and 24 h (P group < 0.01).

The comparisons of attempts, injections, and total sufentanil consumption at 6, 12, 24, and 36 h are presented in Table 4. Attempts, injections, and total sufentanil consumption were different between the two groups. The attempts and injections of background infusion group were significantly lower than those of no background infusion group, and consumption increased significantly (P group < 0.001).

There were no significant differences in I/A, BP and HR between the two groups at 36 h. The background infusion group showed significantly higher satisfaction than the no background infusion group (P<0.001) (Table 5). Bleeding was smaller in the background infusion group at 1 h (P=0.03), without differences at the other time points (all P>0.05) (Table 6).

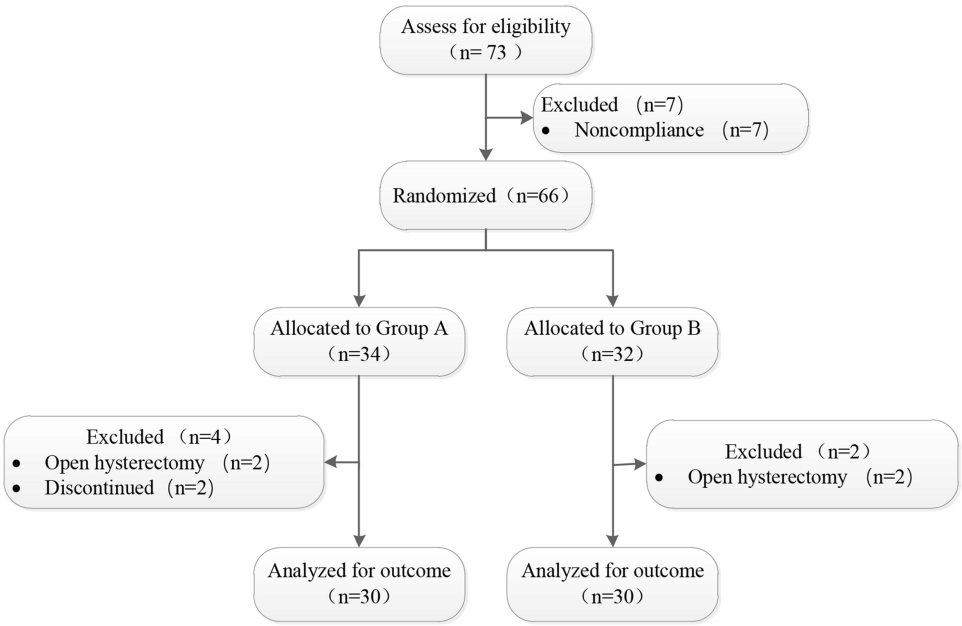

Figure 1 Study CONSORT flow diagram.

Table 1 Baseline Demographic and Obstetric Data

	No Background Infusion Group (n =30)	Background Infusion Group (n =30)	P
Age (years)	27.8±2.8	28.2±2.9	0.56
Height (cm)	162.7±4.5	160.3±5.0	0.06
Weight (kg)	72.6±11.2	71.9±9.2	0.8
BMI (kg/m^2)	27.3±3.7	28.0±3.6	0.49
Operation time (min)	56±7	54±10	0.45
Gestation (weeks)	40±1	40±1	0.89
In-hospital days (day)	4.5±0.8	4.6±1.0	0.14
ASA classification (n)			
I	8	6	0.22
II	22	24	0.18

Abbreviation: BMI, body mass index.

Table 2 VAS Pain Scores 36 h After Surgery for Two Groups

		No Background Infusion Group (n=30)	Background Infusion Group (n=30)	CI 95%	P
Primary outcome	VAS-R 36 h	2.10±1.21	1.76±1.07	−0.3–0.9	0.26
	VAS-U 36 h	1.93±1.28	1.73±1.08	−0.5–0.8	0.58

Note: Values are given as means (range or ±SD).
Abbreviations: CI, confidence interval; VAS-R, visual analog scale – rest; VAS-U, visual analog scale – uterine.

Table 3 VAS Pain Scores 6, 12, 24 After Surgery for Two Groups

		No Background Infusion Group (n=30)	Background Infusion Group (n=30)	P Group	P Time*	P Group*Time#
Secondary outcomes	VAS-R			<0.001		
	6 h	5.36±1.88	3.43±1.22		Ref	<0.001
	12 h	4.06±2.18	2.36±1.40		0.001	<0.001
	24 h	2.66±1.56	2.10±1.15		<0.001	0.084
	VAS-U			<0.01		
	6 h	5.13±2.11	3.73±1.50		Ref	0.005
	12 h	3.93±2.31	2.46±1.47		0.002	0.002
	24 h	2.63±1.60	2.10±1.15		<0.001	0.103

Notes: Values are given as means (range or ±SD). *P time: all time points compared with 6 h. #P group *time: no background infusion compared background infusion at 6 h, 12 h, 24 h.
Abbreviations: CI, confidence interval; VAS-R, visual analog scale – rest; VAS-U, visual analog scale – uterine.

Table 4 Attempts, Injections, and Total Sufentanil Required 6, 12, 24, and 36 h After Surgery for Two Groups

	No Background Infusion Group (n =30)	Background Infusion Group (n =30)	P Group	P Time*	P Group*Time#
Attempts			<0.001		
6 h	0.73±1.01	0.4±0.67		Ref	0.03
12 h	30.56±22.04	2.5±2.97		<0.001	<0.001
24 h	65.76±31.28	5.33±5.49		<0.001	<0.001
36 h	76.60±33.76	7.67±7.96		<0.001	<0.001
Injections			<0.001		
6 h	0.73±1.01	0.40±0.67		Ref	<0.05
12 h	19.53±13.16	2.03±2.10		<0.001	<0.001
24 h	43.26±20.62	4.33±4.22		<0.001	<0.001
36 h	61.56±28.67	5.90±6.39		<0.001	<0.001
Total sufentanil consumption (mcg)			<0.001		
6 h	0.54±0.71	15.38±2.39		Ref	<0.001
12 h	14.6411.21±	35.99±5.21		<0.001	<0.001
24 h	31.7317.59±	72.22±10.69		<0.001	<0.001
36 h	45.23±25.02	107.96±16.03		<0.001	<0.001

Notes: Values are given as mean ± standard deviation. *P time: all time points compared with 6 h. #P group *time: no background infusion compared background infusion at 6 h, 12 h, 24 h, 36 h.
Abbreviation: CI, confidence interval.

Table 5 I/A and Satisfaction 36 h After Surgery for Two Groups

		No Background Infusion Group (n =30)	Background Infusion Group (n =30)	95% CI	P
I/A		0.8±0.2	0.9±0.2	(−0.1, 0.1)	0.6
Satisfaction		4.0±0.9	4.7±0.5*	(−1.1, −0.4)	<0.001
BP	Systolic pressure	113±9.65	116.3±13.67	−9.08, 3.15	0.33
	Diastolic pressure	71.0±7.84	72.93±9.00	–6.2, 2.46	0.39
HR		78.83±4.24	79.06±6.18	−2.97, 1.12	0.87

Notes: Values are given as mean ± standard deviation. *P<0.05 compared with no background infusion group.
Abbreviation: CI, confidence interval.

The minimal respiration rates were not significantly different between the two groups. No patient showed ventilatory depression. The side effects related to sufentanil, including PONV, dizziness, pruritus, headache, and constipation, were not observed in the two groups. All patients had the same Ramsay sedation score.

Table 6 Postpartum Bleeding Within 24 h

Postpartum Bleeding (mL)	No Background Infusion Group (n=30)	Background Infusion Group (n=30)	CI 95%	P
1 h	42.8±19.7	32.8±15.0*	1.0–19.0	0.03
2 h	33.5±23.7	29.0±14.4	−5.7–14.7	0.38
6 h	32.8±24.7	30.0±15.2	−7.8–13.4	0.59
12 h	30.9±27.9	23.7±14.7	−4.3–18.8	0.21
24 h	19.0±12.7	24.0±16.0	−12.5–2.5	0.19

Notes: Values are given as mean ± standard deviation. *P<0.05 compared with no background infusion group.
Abbreviation: CI, confidence interval.

Discussion

This study aimed to investigate the benefit of sufentanil PCIA and background infusion in patients of post-cesarean analgesia. The results suggest that background infusion increased the total consumption of sufentanil within 36 h after cesarean section. Although it did not reduce uterine contraction pain and wound pain at 36 h, it significantly reduced the pain at 6, 12, and 24 h after cesarean section. It improved patient satisfaction and reduced the amount of bleeding after 1 h. Importantly, it did not increase the incidence of PONV and respiratory depression. According to the American Pain Society postoperative guidelines,[7] the use of background infusion is not required because of the aggravation of PONV. Still, one of the conclusions of this study is that the use of background infusion did not increase the incidence of PONV after obstetric surgery. However, a comparative study of the postoperative incidence of PONV requires a sufficient number of samples, and the sample size of this study was very small, and future randomized studies with sufficient sample size are needed.

Opioids are useful and potent analgesics for relieving moderate-to-severe postoperative pain. Morphine, fentanyl, and sufentanil are commonly used opioids for PCIA.[15,24–26] Morphine has been regarded as the first choice for PCIA and is the most used and studied drug for PCIA.[15] Still, the usefulness of morphine is sometimes compromised by its active metabolite (morphine-6-glucuronide) that produces respiratory depression, especially in patients with renal insufficiency because the metabolite is mainly excreted by the kidney.[27] Sufentanil, a selective μ-receptor agonist, is commonly used for PCIA because of its rapid peak, potent analgesic activity, and short half-life.[28,29] Like fentanyl, sufentanil has no active metabolites, and it is 5–10 times more potent than its parent drug, fentanyl.[30,31] Sufentanil displays a lower incidence of respiratory depression than other opioids.[24,32] Sufentanil has a relatively rapid equilibration half-life ($t_{½}$ of 6.2 minutes) between plasma and brain, compared to 2.8 h for morphine,[33,34] and a relatively shorter duration of action than morphine and fentanyl.[35] Sufentanil transfer into milk has not been reported. Still, its safety profile is likely similar to fentanyl, and it is unlikely to cause any appreciable effects by its low levels in breast milk.[36] Based on these properties, sufentanil can be appropriate and suited for PCIA. It is the most commonly used opioid for PCIA in China,[25,37] is now widely used for surgery patients during anesthesia, and has also been extensively used in postoperative pain control and labor pain relief.[38–40]

A study showed that the dose of 2.5 μg/kg of sufentanil with background infusion is preferred because of better pain alleviation without an increase of adverse effects up to 48 h after surgery.[16] Combined with our work experience, the dose of sufentanil was set at 2.0 μg/kg in the present trial. Still, improved pain control was observed for the first 24 h when using background infusion. It was also observed in abdominal and thoracic surgeries.[17,18] Uterine contraction pain is defined as the intermittent cramping pain associated with uterine contraction. Wound pain is defined as the constant and evoked pain over the wound and adjacent region. Postcesarean pain, unlike most postoperative pain, consists of a nociceptive barrage from the incisional wound and uterine contraction.[41] In this study, both types of pain were scored together. Because the pain of uterine contractions is enough to cover the wound pain, it was found in the study that many patients could not distinguish between the pain of the two, resulting in the same pain score. This study showed that the VAS at 6 h after surgery was higher in the two groups, which may be related to the inability to effectively reduce the pain of uterine contraction by using sufentanil alone. Hsu et al[41] reported that 20 mg tenoxicam significantly potentiated

morphine PCIA by reducing uterine cramping pain. Uterine contractions can reduce postpartum bleeding, and postpartum hemorrhage is one of the serious complications of cesarean section, and massive hemorrhage is the direct cause of hysterectomy and maternal death.[42] This study found that the background infusion group had significantly reduced pain from uterine contractions but also reduced the amount of bleeding 1 h after surgery, directly reducing the adverse reactions of postpartum bleeding.

Apfel et al[43] showed that patients with a history of motion sickness or PONV. Therefore, such patients were excluded. Although the American Pain Society suggests that background infusion of opioids is associated with an increased risk of nausea and vomiting, the present showed that PONV was not observed in the two groups. Regarding patients who use opioids after cesarean section, the reason for the extremely low incidence of PONV deserves further study. This may be the reason why the sample size of this study is very small. There have been attempts to create a score that could be used to rate the severity of nausea, vomiting, and retching in patients undergoing chemotherapy.[44,45] Still, no score or index has been validated to define clinically important PONV. Techniques used in the past to measure PONV have included absolute counts or incidence rates, Likert scales, VASs, and treatment response. Wengritzky et al[45] proposed the VAS as a screening tool in the clinical setting for rapid assessment or audit tool, and the VAS was selected in this study.

A lower I/A indicates a higher number of patient attempts occurring for each injection. It may indicate inadequate pain control. Besides, Sinatra et al[46] suggest that lower I/A ratios may reflect a delay in obtaining the peak analgesic effect. In the present study, there was no difference in the I/A ratio between the two groups.

This study has limitations. It was performed at only one center, possibly introducing bias due to local practices and limiting the generalizability of the results. Comparisons with other analgesics or doses of sufentanil were not performed.

Conclusion

Compared with no background infusion, the total consumption of sufentanil at 36 h postoperative was greater in the background infusion group. Although uterine contraction pain and wound pain at 36 h were not reduced, background infusion significantly reduced the pain at 6, 12, and 24 h after cesarean section. It improved patient satisfaction and reduced the amount of bleeding after 1 h. Importantly, it did not increase the incidence of PONV and respiratory depression.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

After approval from the ethics committee of Shanxi Bethune Hospital (#YXLL-SL-2020-017), consenting parturients were included in this prospective randomized study. Written informed consent was obtained from all subjects.

Clinical Trials

The study was registered prior to patient enrollment at the Chinese Clinical Trial Register (Register number: ChiCTR2000037940), participating in the World Health Organization International Clinical Trials Registry Platform.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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