Randomized Controlled Trial

Effect of Epidural Volume Extension Using Low-Dose Sufentanil Combined with Low-Concentration Ropivacaine on Visceral Pain During Cesarean Sections: A Randomized Trial

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Background: Visceral pain is common in cesarean sections conducted under combined spinal-epidural anesthesia (CSE). Epidural volume extension (EVE) is a technique for enhancing the effect of intrathecal blocks by inducing epidural fluid boluses in the CSE. Whether EVE that uses different drugs can reduce visceral pain during cesarean sections is rarely studied.

Objectives: In this study, we compared the effect of EVE that used low-dose sufentanil, either alone or combined with low-concentration ropivacaine, on visceral pain during cesarean sections under CSE.

Study Design: A prospective, randomized controlled study.

Setting: The study was performed in the Jiaxing University Affiliated Women and Children Hospital.

Methods: We randomly allocated 100 healthy patients to 4 groups to receive spinal hyperbaric bupivacaine followed by EVE with 10 mL of 0.9% saline (Group NS), 10 mL of 0.15% ropivacaine (Group R), 10 mL of 10 μg sufentanil (Group S), or a combination of 10 mL of 0.15% ropivacaine and 10 μg sufentanil (Group RS) through the epidural catheter 15 minutes thereafter. The primary outcome was the incidence of visceral pain. Each occurrence of visceral pain during the procedure was recorded. Every patient's pain level was evaluated on the visual analog scale (VAS). The consumption of sufentanil during patient-controlled intravenous analgesia (PCIA) and patient satisfaction scores under anesthesia were recorded within 48 hours after surgery. Maximum sensory block levels, segmental increases after EVE, time for sensory regression to the tenth thoracic dermatome (T10), and time for motor recovery to modified Bromage 0 were compared among each group.

Results: Visceral pain occurred in 60% (15/25), 56% (14/25), 24% (6/25) and 12% (3/25) of patients in the NS, R, S, and RS groups, respectively. The incidence of visceral pain was significantly lower in the RS group than in the NS or R groups ($P < 0.05$) but not significantly different from the S group. The S and RS groups have significantly lower VAS scores compared to the NS and R groups ($P < 0.05$). Sufentanil consumption during PCIA in the R and RS groups was significantly lower than in the NS group. Patients' overall intraoperative satisfaction scores were significantly higher in the S and RS groups than in the NS or R groups.

Limitations: This study has limitations in its sample size, time point of EVE implementation, absence of laboratory indicators, and lack of assessment of postoperative visceral pain, necessitating future studies to address these issues.

Conclusions: EVE at 15 minutes after spinal anesthesia with a 10 mL combination of low-dose sufentanil (10 μg) and low-concentration (0.15%) ropivacaine can effectively reduce the incidence and severity of visceral pain in cesarean sections under CSE. At the same time, using EVE in this way can reduce postoperative opioid consumption and improve intraoperative satisfaction.

Key words: Sufentanil, ropivacaine, visceral pain, epidural volume extension (EVE), cesarean

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The combined spinal-epidural anesthesia (CSE) technique for cesarean sections has been used widely in some obstetric hospitals (1). However, despite adequate levels of sensory block, some parturients require supplemental analgesics to relieve the pain associated with traction on the abdominal viscera (2-4).

Epidural volume extension (EVE) is a modification of CSE in which a drug or saline solution is injected into epidural space after the intrathecal block to increase the spread of drugs given intrathecally. It has been shown that EVE can extend a spinal block and provide adequate anesthesia for a cesarean section while allowing faster motor recovery of the lower limbs (5-8). EVE's improvement of sensory diffusion and shortening of motor recovery time were mainly due to volume effect rather than drug effect (6,7,9-11). Nonetheless, studies have shown that using different anesthetic mixtures for EVE may also lead to different effects, such as 0.25% bupivacaine reducing intraoperative pain more effectively than saline (7). We speculate that in addition to volume effects, EVE has pharmacological effects that may reduce visceral pain. To confirm this hypothesis, we conducted this study.

Epidural analgesia with low concentrations of local anesthetics and low-dose opioids has been used for labor pain relief without affecting motor function (12,13). Ropivacaine is a long-acting local anesthetic with a marked differential blockade between sensory and motor fibers (14). Sufentanil, a highly fat-soluble opioid, can be used safely in epidural space (15) and is a powerful agonist of the opiate receptor (16). Unlike myelinated A-delta fibers, which transmit incisional pain, visceral pain is thought to be transmitted by unmyelinated C fibers. Opioids such as sufentanil depress C-fiber-mediated responses. In addition, spinal μ-and-δ-opioid receptors have a significant role in the modulation of visceral nociception (17).

We hypothesized that EVE using low concentrations of local anesthetics or low-dose sufentanil could reduce visceral pain. Our primary outcome was the incidence of visceral pain. To the best of our knowledge, this study represents the first attempt to compare the effects of using different anesthetic mixtures in EVE on visceral pain during cesarean section under CSE.

Methods

Patients

This study was approved by the ethics committee of Jiaxing University Affiliated Women and Children's Hospital (batch no. TG2018-02) and was registered at the Chinese Clinical Trials Registry (ChiCTR1800016281). Written informed consent was obtained from all patients involved in the trial. The study was performed in accordance with the principles stated in the Declaration of Helsinki.

From June 2018 to June 2019, 100 patients who had an ASA physical status of I or II, were aged 18-40 years, and were scheduled to undergo elective cesarean sections under CSE in our hospital were enrolled in this study. Exclusion criteria were contraindications to regional anesthesia, pregnancy-induced hypertension, bleeding disorders, a gestational age under 36 weeks, and refusal to participate in the trial.

Patients were randomly assigned to one of 4 groups based on a computer-generated random number sheet. All patients were unaware of their group assignments. The randomization scheme and epidural injection solutions were prepared by an investigator who was not involved in the patients' pain management and data collection. The randomization scheme was kept in sequentially numbered opaque envelopes, one of which was opened for each patient enrolled. The syringe containing the solution for the EVE is covered with opaque tape. An anesthesiologist who was unaware of the patient group allocation performed CSE and EVE, and an anesthesia nurse, who was also unaware of the patient group allocation, collected preoperative and intraoperative data.

Anesthesia and Data Collection

All patients received spinal anesthesia using hyperbaric 0.5% bupivacaine. EVE was performed 15 minutes later through the epidural catheter. Group NS received 10 mL of 0.9% saline, Group R received 10 mL of 0.15% ropivacaine, Group S received 10 mL of 10 μg sufentanil, and Group RS received 10 mL of 0.15% ropivacaine and 10 μg sufentanil.

After the patients entered the operating room, electrocardiography (ECG), heart rate (HR), noninvasive blood pressure (BP) and pulse oximetry (SpO_2) were routinely measured and recorded for all patients. The baseline BP and HR were measured. All patients were preloaded intravenously with 500 mL of lactated Ringer's solution.

The CSE block was performed using an 18-gauge Tuohy needle in the left lateral position of the patient at L3-4 interstitial space. We confirmed epidural space by loss of resistance to saline. A 25-G Whitacre spinal

needle was introduced through the Tuohy needle into the subarachnoid space and observed for flow of cerebrospinal fluid (CSF). Then all patients received spinal anesthesia through hyperbaric 0.5% bupivacaine with the bevel facing cephalad. The dose of hypobaric bupivacaine was evaluated based on a decision support model that we previously developed. The model was Y=0.5922+0.055117* X1-0.017599* X2 (Y: bupivacaine volume; X1: vertebral column length; X2: abdominal girth) (18). The spinal needle was withdrawn, and an epidural catheter was inserted 3 cm into the epidural space through the Tuohy needle, followed by a confirmed negative aspiration of blood and cerebrospinal fluid. Then patients were immediately placed in supine positions with a 15° left lateral tilt and the blood pressure measured every 2.5 minutes until delivery and then every 5 minutes until the completion of surgery. After 15 minutes, the premixed solution was injected through the epidural catheter according to the group allocation.

The spinal spread was assessed in both midclavicular lines by an 18-gauge needle for loss of pinprick discrimination at 10, 15, 20, 25, 30, 35, and 40 minutes after spinal injection, based on a dermatological chart. If the sensory block levels of both sides differed, the average value was used in the analysis. Operations were initiated when the blockade was extended to T6. If the sensory blockade was not obtained to T6 15 minutes after spinal injection, supplemental 2% lidocaine was administered through the epidural catheter until the sensory blockade reached to T6, and the patient was excluded. Patients were also excluded if their sensory block levels were higher than T4 within 15 minutes.

Outcome

The primary outcome measure was the incidence of intraoperative visceral pain. Pain associated with exteriorization of the uterus and traction of the peritoneum was defined as visceral pain. All patients were instructed to tell the investigator promptly if they felt visceral pain. As soon as the patient complained of visceral pain, it was recorded. The secondary outcome measures were the severity of visceral pain, consumption of sufentanil during PCIA, and patient satisfaction scores with anesthesia. Maximum sensory block level, segmental increase after EVE, and adverse effects such as hypotension, bradycardia, nausea and vomiting, shivering, respiratory depression, and pruritus were also recorded. Apgar scores were assessed instantly at one and 5 minutes after fetal delivery. The value of visceral pain was indicated by the patient, using a 10 cm VAS. A value of 3-6 was considered moderate pain, and > 6 was severe pain. Motor function was assessed at 2-minutes intervals with use of the modified Bromage score (1 = able to raise legs above table, 2 = able to flex knees, 3 = able to move feet only, 4 = no movement in legs or feet).

If patients suffered from moderate to severe visceral pain (VAS $\geq$ 3), 5 μg of sufentanil was administered intravenously after fetal extraction. If patients complained of nausea or vomiting, 5 mg tropisetron was given as an antiemetic. Bradycardia was defined as HR < 60 bpm and was treated with 0.25 mg of atropine intravenously. Any episode of hypotension, defined as systolic BP < 90 mmHg or > 20% decline from the baseline BP, was treated with 50 μg of phenylephrine and repeated as needed. Respiratory depression was defined as SpO_2 < 95% or respiratory rate < 10 breaths/minute and treated with increased oxygen inhalation or respiratory support if needed.

In the immediate postoperative period, the level of sensory block and the degree of motor block were assessed at 15-minute intervals until complete recovery from anesthesia.

Postoperatively, all patients were provided with patient-controlled intravenous analgesia (PCIA) in the form of sufentanil for 48 hours. PCIA protocols were 150 μg of sufentanil diluted in 150 mL of normal saline. PCIA parameters were set at a 2 mL bolus with a lockout time of 15 minutes and 2 mL/h baseline infusion. The PCIA bolus dose was administered on patient request. The consumption of sufentanil during 48 hours after surgery was recorded. All patients were invited to rate their overall satisfaction with anesthesia by using a 4-point scale (1-not satisfied, 2-moderately satisfied, 3-satisfied, and 4-very satisfied) 48 hours after surgery.

Sample Size Estimation

The sample size was calculated using PASS software version 15.0 (NCSS, LLC). In our pilot study, we used the same grouping as in this study, with 10 patients in each group, and underwent the same anesthesia procedure as in this study. Based on the results of the pilot study, visceral pain relief was expected to be 80% for Group RS, 80% for Group S, 40% for Group R, and 30% for Group NS. We determined that a sample size of 67 patients would provide 90% power at a 2-sided α level of 0.05 to detect a difference in the groups. Considering a dropout rate of 20%, a total sample size of 100 was determined, with 25 patients per group.

Statistical Analysis

We used the Kolmogorov–Smirnov test to assess whether the continuous variables were normally distributed. Data were analyzed using one-way ANOVA or the Kruskal–Wallis test, followed by Bonferroni correction for post hoc analyses for multiple comparisons. Dichotomous data, such as the incidence of visceral pain, were analyzed using the Cochran-Armitage χ^2 test for trend. If the overall test of difference among groups was significant, chi-squared tests were used for pairwise comparisons. Analyses were performed using IBM® SPSS® Statistics for Windows version 23.0 (IBM Corp.) and GraphPad Prism version 9.1.2 (GraphPad Software Inc.). *P* values < 0.05 were considered statistically significant (2-sided).

Results

Initially, 109 patients were enrolled and checked for eligibility. Five patients declined to participate in this clinical trial, and 4 patients were excluded from the analysis because their sensory block levels did not reach T6 (Fig. 1). No inter-group differences were noted in demographic, obstetric, and surgical characteristics. There was no difference among the 4 groups in maximum level of sensory blocks, segmental increase of sensory blocks after EVE, time for sensory regression to T10, or time for motor recovery to modified Bromage 0 ($P > 0.05$, Table 1).

Visceral pain occurred in 60% (15/25), 56% (14/25), 24% (6/25) and 12% (3/25) of patients in the NS, R, S, and RS groups, respectively. The incidence of visceral pain and intravenous sufentanil rescue analgesia was significantly lower in the RS group than in the NS or R groups ($P < 0.05$) but not significantly different from Group S ($P > 0.05$). The S and RS groups had significantly lower VAS scores than did the NS and R groups ($P < 0.05$, Table 2).

There were significant differences in PCIA sufentanil consumption among the 4 groups within 48 hours after surgery, with cumulative PCIA doses in the R and RS groups significantly lower than in the NS group. Patients' overall intraoperative satisfaction scores were significantly higher in the S and RS groups than in the NS or R groups (Table 3).

Adverse effects and neonatal outcomes are presented in Table 4. The incidence of maternal adverse effects such as hypotension, nausea or vomiting, and shivering were similar among the groups, as was the use of ephedrine. None of the mothers experienced opioid-related adverse effects such as bradycardia, respiratory depression, and pruritus. We also found no significant differences in neonatal Apgar scores among the groups.

Discussion

In this prospective, randomized, double-blind study, we found that, compared with an epidural injection of an equal volume of saline or ropivacaine alone, a combination of 10 mL of 0.15% ropivacaine and 10 μg sufentanil for EVE reduced the incidence of visceral pain significantly. Ten mL of 0.15% ropivacaine combined with 10 μg sufentanil or 10 μg sufentanil alone for EVE reduced the severity of visceral pain and improved patient satisfaction during caesarean sections under CSE.

Even with an adequate level of sensory block, many patients will experience unpleasant sensations during the exteriorization of the uterus and traction of abdominal organs (19) and then require rescue analgesia, which is commonly administered intravenously with opioids. However, intravenous use of opioids may cause side effects such as respiratory depression, nausea and vomiting, or chest wall rigidity. The interval between delivery and the onset of visceral pain was short, so we considered using EVE to accelerate the segmental increase. EVE is thecal compression due to volume effects caused by epidural infusion of fluid. This thecal compression causes the local anesthetics in the CSF to shift headward, raising the level of sensory block (20).

We observed lower VAS scores and higher patient satisfaction in both of the study groups who used sufentanil. At the same time, the incidence of visceral pain and the number of rescue analgesics were significantly lower in the combination group. There was a decrease in these rates among patients receiving sufentanil alone, but the difference was not statistically significant. The reason for this phenomenon might have been that the dose of sufentanil we used was too small. In a randomized controlled study, Qiang Lu et al (21) recommended the use of a higher dose of sufentanil (15-20 μg) in epidural injection to reduce the occurrence of visceral pain during cesarean sections. However, Qiang Lu et al also pointed out that further increasing the dose would cause more side effects such as nausea, vomiting, and hypotension. In our study, the combination of low-dose sufentanil and low-concentration ropivacaine showed significantly better efficacy. Therefore, we can conclude that combination therapy can use lower doses and concentrations to produce reliable efficacy.

The consumption of PCIA sufentanil within 48 hours

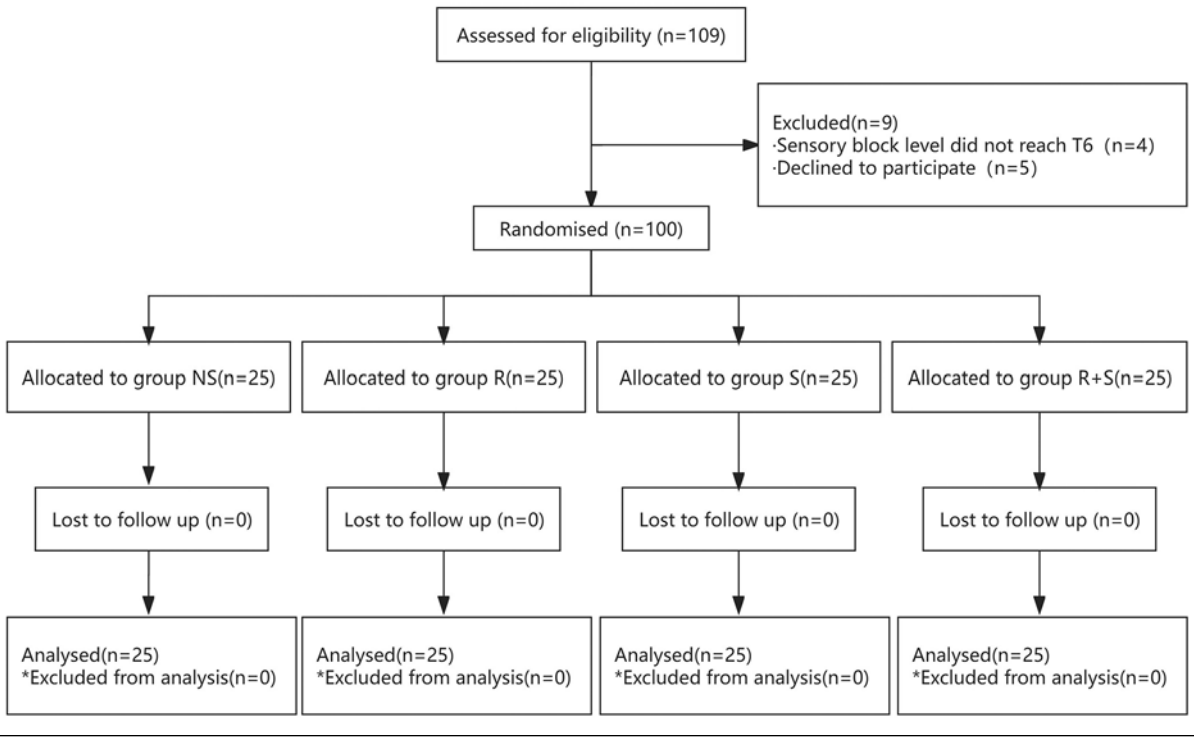

Fig. 1. *Consort flow diagram.*

Table 1. *Demographic and obstetric characteristics, duration of surgery, blood loss, dose of bupivacaine, Apgar scores and anesthetic characteristics.*

	NS (n = 25)	R (n = 25)	S (n = 25)	RS (n = 25)	*P*
Age (yr)	31.92 ± 4.35	30.16 ± 4.22	29.24 ± 3.70	31.48 ± 4.87	0.114
Height (cm)	160.68 ± 4.12	159.76 ± 5.52	159.50 ± 4.69	160.24 ± 3.56	0.805
Weight (kg)	70.71 ± 8.54	71.09 ± 8.65	70.95 ± 13.59	69.67 ± 8.73	0.960
Parity					
Nulliparous (%)	6 (24)	4 (16)	8 (32)	6 (24)	0.625
Multiparous (%)	19 (76)	21 (84)	17 (68)	19 (76)	
The volume of 0.5% hyperbaric Bupivacaine (mL)	2.0 (1.8,2.3)	2.0 (1.7,2.2)	2.0 (1.8,2.2)	2.0 (1.9,2.2)	0.538
Duration of surgery (min)	52.92 ± 8.57	51.48 ± 8.49	48.92 ± 7.70	49.88 ± 7.08	0.306
Blood loss (ml)	272.80 ± 99.98	264.00 ± 75.72	286.00 ± 88.41	252.00 ± 56.79	0.515
Maximum sensory block level	T4 (T3-T5)	T4 (T3.5-T5)	T4 (T3-T4)	T3 (T3-T4)	0.112
Segmental increase after EVE	1.00 ± 0.91	0.84 ± 0.69	0.88 ± 0.93	1.16 ± 0.55	0.478
Time for sensory regression to T10 (min)	112.80 ± 16.84	104.40 ± 17.04	108.00 ± 16.20	108.60 ± 15.17	0.349
Time for motor recovery to Modified Bromage 0 (min)	193.20 ± 33.91	187.80 ± 27.08	201.20 ± 33.14	193.80 ± 31.20	0.516

Data are mean ± SD, number (%), or median (IQR).

after surgery in the 2 groups who used ropivacaine was similar to that of the group who used sufentanil alone but significantly lower than that of the normal saline group. We inferred that using low-concentration ropivacaine alone or in combination with low-dose sufentanil for EVE could significantly reduce postoperative pain after cesarean sections, and the main effect might have been related to the blocking of the transmission of nociceptive stimuli by ropivacaine, which prevented pain sensitization (22).

Table 2. *Incidence of visceral pain, VAS score, and sufentanil add-on rate.*

	NS (n = 25)	R (n = 25)	S (n = 25)	RS (n = 25)	*P*
visceral pain (%)	15 (60)	14 (56)	6 (24)	3 (12) [ab]	< 0.001
VAS scores	2.0 (0.0,5.0)	2.0 (0.0,4.5)	0.0 (0.0,0.0) [ab]	0.0 (0.0,1.0) [ab]	< 0.001
The number of rescue analgesics (%)	12 (48)	11 (44)	4 (16)	1 (4) [ab]	0.001

Data are presented as number (%) or median (IQR). [a]$P < 0.05$ vs. Group NS, [b]$P < 0.05$ vs. Group R.

Table 3. *PCIA-delivered cumulative sufentanil consumption and parturients' satisfaction scores.*

	NS (n = 25)	R (n = 25)	S (n = 25)	RS (n = 25)	*P*
PCIA-delivered cumulative sufentanil consumption (μg)	105.16 ± 15.22	87.84 ± 23.38[a]	91.84 ± 20.02	82.80 ± 22.47[a]	0.002
Parturients' satisfaction score	3.0 (1.0,4.0)	3.0 (2.0,4.0)	4.0 (3.5,4.0) [ab]	4.0 (4.0,4.0) [ab]	0.002

Data are presented as mean ± SD or median (IQR). [a]$P < 0.05$ vs. Group NS, [b]$P < 0.05$ vs. Group R.

Table 4. *Hemodynamic changes, side effects, ephedrine use and neonatal outcome.*

	NS (n = 25)	R (n = 25)	S (n = 25)	RS (n = 25)	*P*
Hypotension	8 (32.0)	11 (44.0)	13 (52.0)	9 (36.0)	0.486
Bradycardia	0	0	0	0	-
Nausea or vomiting	11 (44.0)	9 (36.0)	7 (28.0)	2 (8.0)[†]	0.034
Shivering	8 (32.0)	7 (28.0)	5 (20.0)	5 (20.0)	0.696
Respiratory depression	0	0	0	0	-
Pruritus	0	0	0	0	-
Ephedrine use (mg)	2.16 ± 3.41	4.56 ± 6.07	4.32 ± 5.88	4.08 ± 6.42	0.410
1 min Apgar score	9.0 (8.5,10.0)	9.0 (8.5,10.0)	9.0 (8.5,10.0)	9.0 (8.0,10.0)	0.964
5 min Apgar score	10.0 (9.0,10.0)	10.0 (9.0,10.0)	10.0 (9.0,10.0)	10.0 (9.0,10.0)	0.956

Data are mean ± SD, number (%), or median (IQR). † $P < 0.05$ vs. Group NS.

In our study, there were no significant differences in EVE characteristics such as maximum level of sensory blocks, segmental increase of sensory blocks after EVE, time for sensory regression to T10, or time for motor recovery to modified Bromage 0 between the groups. As stated above, the effect of EVE on the level of blockade is mainly due to volume effects rather than drug effects. At the same time, low-dose sufentanil and low-concentration ropivacaine do not have a significant effect on movement, so they do not cause delayed motor recovery.

Other side effects were not significantly different among the groups. Nor did the incidence of hypotension and the amount of ephedrine used differ significantly among the groups. These findings are consistent with the results of Heesen M et al and can be simply understood, since the same volume of fluid was used for EVE in each group in our study, resulting in a similar level of blocks (5,6,23,24). There were no opioid-related side effects such as bradycardia, respiratory depression, or pruritus in each group. There were also no neonates with Apgar scores lower than 8. These results agree with previous studies (5-8, 12, 13). The incidence of nausea and vomiting was significantly lower in the RS group, which we believe is because nausea and vomiting during cesarean sections are closely related to the occurrence of visceral traction pain.

In our study, we were unable to prove that using low-concentration ropivacaine alone for EVE had beneficial effects on the incidence of visceral pain during cesarean sections. To reduce the incidence of visceral pain, using opioids in the EVE solution is still essential. However, it is reassuring that the use of low-dose sufentanil did not increase opioid-related side effects.

Limitations

There are multiple limitations to this study. First, some data collected in this study is observational rather than based on laboratory indicators such as norepinephrine, interleukin-6 (IL-6), or Prostaglandin E2 (PGE2), which could have led to documentary bias. By applying strict blinding and explicit VAS scores, the authors have made efforts to minimize bias. Second, the comparison of side effects is not robust enough, since this study is not specifically designed for it. Third, we set the time of EVE at 15 minutes after spinal anesthesia, and EVE may

have different effects at different time points, which is worth further study. Finally, we did not assess visceral pain after surgery, which constitutes a limitation to the comprehensiveness of this study.

Conclusion

In summary, EVE with 10 mL of low-dose sufentanil (10 μg) and low-concentration (0.15%) ropivacaine can effectively reduce the incidence and severity of visceral pain during cesarean sections under CES. EVE induced with the quantities of the aforementioned substances can reduce postoperative opioid consumption and improve intraoperative satisfaction. Our study showed that the combination of sufentanil and ropivacaine was more effective than was either substance alone.

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