



# The Analgesic Effect of Different Concentrations of Epidural Ropivacaine Alone or Combined With Sufentanil in Patients After Cesarean Section

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**Background:** Patients experience moderate-high intensity postoperative pain after cesarean section (CS). The aim of this study was to investigate the optimal concentrations of ropivacaine and sufentanil for use in controlling pain after CS.

**Methods:** One hundred and seventy-four women undergoing elective CS were randomly allocated to four groups. Epidural analgesia was administered with 0.1% ropivacaine in the R<sub>1</sub> group, 0.15% ropivacaine in the R<sub>2</sub> group, a combination of 0.1% ropivacaine and 0.5 µg/ml of sufentanil in the R<sub>1</sub>S group, and a combination of 0.15% ropivacaine and 0.5 µg/ml of sufentanil in the R<sub>2</sub>S group (at a basal rate of 4 ml/h, bolus dose of 4 ml/20 min as needed). Pain scores (numerical rating scale [NRS]: 0–10 cm) at rest (NRS-R), during movement (NRS-M), and when massaging the uterus (NRS-U) were documented at 6 and 24 h. We also recorded patient satisfaction scores, time to first flatus, motor deficits, and adverse drug reactions.

**Results:** NRS (NRS-R, NRS-M, NRS-U) scores in the R<sub>2</sub>S group (2 [1–3], 4 [3–5], 6 [5–6], respectively) were lower than in the R<sub>1</sub> group (3 [3–4], 5 [4–6], 7 [6–8], respectively) ( $p < 0.001$ ,  $p < 0.05$ ,  $p < 0.01$ , respectively) at 6 h; and patient satisfaction (9 [8–10]) was improved compared to the R<sub>1</sub> group (8 [6–8]) ( $p < 0.01$ ). The time to first flatus (18.7 ± 11.8 h) was reduced relative to the R<sub>1</sub> group (25.9 ± 12.0 h) ( $p < 0.05$ ). The time to first ambulation was not delayed ( $p > 0.05$ ). However, the incidence of pruritus (4 [9.3%]) was increased compared to the R<sub>2</sub> group (0 [0]) ( $p < 0.05$ ) at 6 h, and the incidence of numbness (23 [53.5%], 23 [53.5%]) was increased compared to the R<sub>1</sub> group (10 [23.3%], 10 [23.3%]) (all  $p < 0.01$ ) at both 6 and 24 h.

**Conclusions:** Although we observed a higher incidence of pruritus and numbness, co-administration of 0.15% ropivacaine and 0.5 µg/ml of sufentanil administered epidurally optimized pain relief after CS, with treated subjects exhibiting lower NRS scores, shorter time to first flatus, and higher patient-satisfaction scores.

**Keywords:** cesarean section, postoperative pain, analgesia, sufentanil, ropivacaine

## INTRODUCTION

A surfeit of cesarean sections are performed annually worldwide. In 2016, the cesarean section (CS) rate was 31.9% (Martin et al., 2017) and 41.1% (Liang et al., 2018) in the United States and China, respectively. Despite the numerous measures used to manage pain, the incidence of inadequate analgesia after CS remains nearly 50% (Patel et al., 2017). Pain relief after CS is crucial, as poor pain relief can interfere with breast feeding and delay infant weight gain (Hirose et al., 1996). Inadequate analgesia can impair functions such as ambulation and dietary intake, and lead to complications such as thromboembolism (Leung, 2004) and postoperative ileus (inhibition of gastrointestinal motility after surgery that prevents oral intake) (Cho et al., 2017). Poor pain relief may even lead to chronic pain (Jin et al., 2016) and increased postpartum depression (Shen et al., 2020). Therefore, effective pain management after CS continues to be a relevant public health issue.

The search for the ideal method to manage postoperative pain is ongoing. Although the use of opioids is the gold standard (Kerai et al., 2017), the effects of opioids on lactation have limited intravenous opioid use—especially long-term use. Wu et al. found that patient-controlled epidural analgesia (PCEA) provided significantly superior analgesia compared with intravenous patient-controlled analgesia (PCIA) (Wu et al., 2005). Epidural morphine is commonly used for analgesia after CS (Carvalho and Butwick, 2017), but can produce a high incidence of pruritus, nausea, and vomiting (Youssef et al., 2014). These adverse drug reactions (ADRs) are difficult to prevent, and therefore modified regimens such as low concentrations of local anesthetics together with other opioids have been advocated to reduce opioid dosage and thereby decrease the incidence of bothersome ADRs. Epidural opioids also reduce the dosage of local anesthetics. A study by Gogarten et al. found that when combined with ropivacaine, sufentanil can reduce the concentration of ropivacaine required and the degree of motor blockade (Gogarten et al., 2004).

Ropivacaine has been used in labor for epidural analgesia and post-cesarean analgesia because of its lower potential for accumulation, greater sensorimotor-differential block, and increased cardiovascular safety profile (Bullingham et al., 2018; Wang et al., 2019). The breast milk/plasma concentration ratio of ropivacaine was lower than bupivacaine when administered epidurally after CS (Matsota et al., 2009), which is essential for neonatal safety. Although ropivacaine co-administered with sufentanil successfully reduced postoperative pain, few investigators have thus far evaluated the optimal concentration necessary. Therefore, we evaluated the analgesic effects by using two different concentrations (0.1% and 0.15%) of ropivacaine with or without 0.5 µg/ml of sufentanil to relieve post-cesarean pain.

## MATERIALS AND METHODS

This trial was conducted at the Department of Anesthesiology, Xuanwu Hospital of Capital Medical University in China. Ethics

approval (ea1/185/10) was obtained from the ethics committee of the Xuanwu Hospital of Capital Medical University. The trial was registered with the Chinese clinical trial registry (ChiCTR 1900 021740), and written informed consent was obtained on the day before surgery.

Our primary aim was to compare the analgesic efficacy of the four groups at the first 24 h after CS by a prospective, randomized, double-blinded clinical trial. Our secondary objective was to compare patient satisfaction, gastrointestinal symptoms, postsurgical recovery, and ADRs among the four groups.

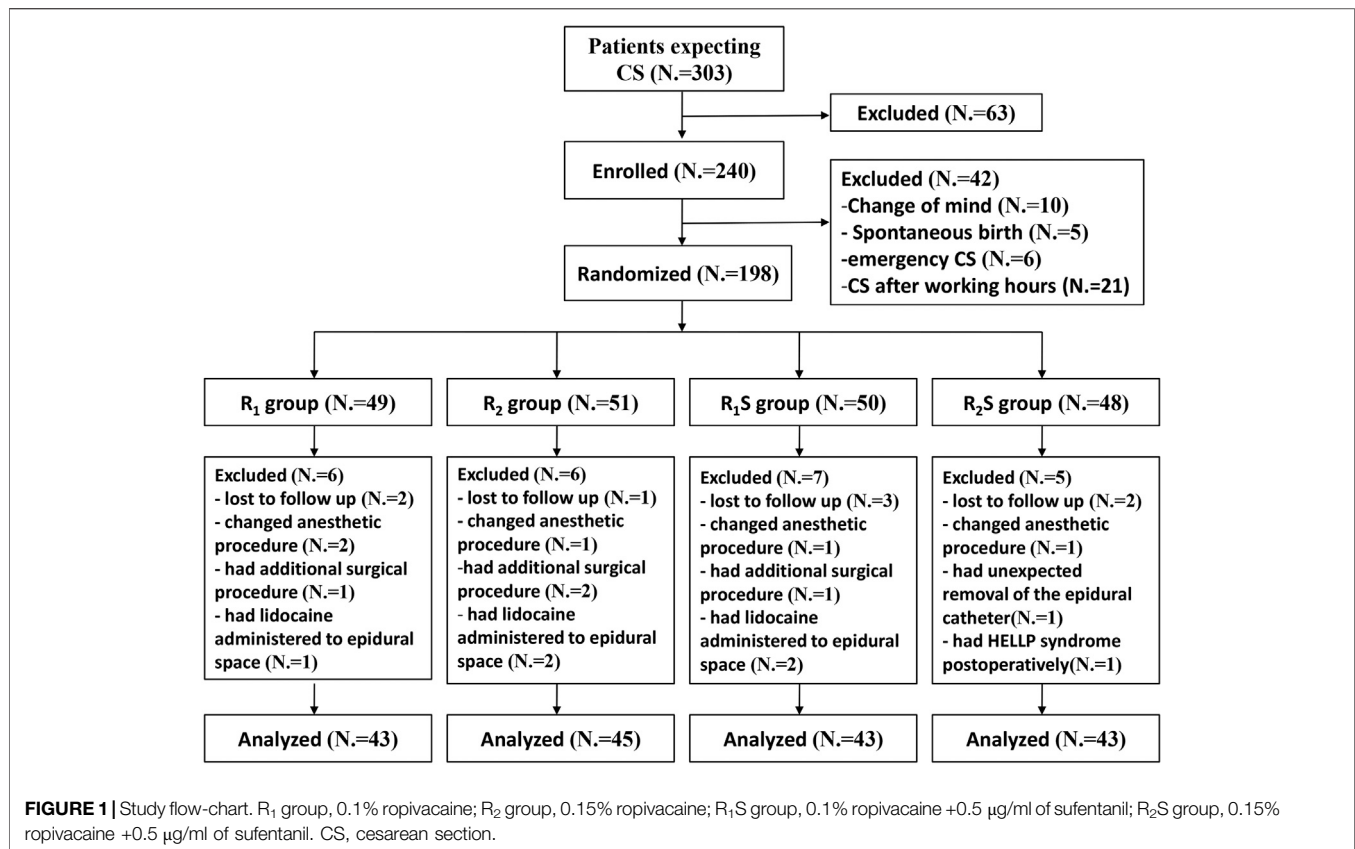
## Participants

This trial included 174 women who were enrolled from March 2019 to September 2019. Women were eligible for inclusion if they were 21–45 years of age after 32 weeks of gestation (If the gestational age is less than 32 weeks, the newborn will be transferred to the children's hospital, which may affect the mother's mood) and at the American Society of Anesthesiology physical status classification I–II (Matsota et al., 2011), and were scheduled to undergo CS under neuraxial anesthesia. Patients with a known allergy to sufentanil and/or local anesthetics; a history of chronic pain, chronic opioid use, anxiolytic medication use, or drug and/or alcohol abuse; showing contraindications for neuraxial anesthesia; or manifested eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes and low platelet count), or hemostatic disorders were excluded.

## Study Protocol

After pre-hydration with 500 ml of lactated Ringer's solution, women underwent combined spinal-epidural anesthesia (CSEA) at the L2–L3 or L3–L4 spinal interspace in the right lateral position, receiving an injection containing between 7.5 and 10 mg of 0.5% hypobaric bupivacaine (Shanghai Harvest Pharmaceutical, Shanghai, China), depending upon their height (for a height <155 cm, 7.5 mg was administered; 155–160 cm, 8 mg; 160–165 cm, 8.5 mg; 165–170 cm, 9 mg; 170–175 cm, 9.5 mg; and >175 cm, 10 mg). After intrathecal injection, the epidural catheter was inserted up to 3 cm into the epidural space, and then patients were placed in a supine position in a left-lateral tilt. Once a bilateral sensory block to the T4 dermatome was achieved (which we tested by pinprick), the operation began. If sensory block was not achieved to the T4 level, 2% lidocaine (Shanghai Harvest Pharmaceutical, Shanghai, China) was administered into the epidural space to achieve adequate anesthesia, and the patients were excluded from further analysis.

Before skin closure, a 3-ml 2% lidocaine solution was administered into the epidural space to confirm adequate placement of the epidural catheter, and a CADD™ Administration set, Model 6,300 (Smiths Medical, St Paul, MN, United States), was then connected to each patient. Patients were randomized to the receipt of a continuous epidural infusion with PCEA of one of the four solutions using the sealed-envelope technique: a R<sub>1</sub> group, 0.1% ropivacaine (AstraZeneca AB, Sodertalje, Sweden); a R<sub>2</sub> group,



0.15% ropivacaine; a R<sub>1</sub>S group, 0.1% ropivacaine +0.5 µg/ml of sufentanil (Yichang Humanwell pharmaceutical, Hubei, China); and a R<sub>2</sub>S group, 0.15% ropivacaine +0.5 µg/ml of sufentanil. Dosage was a 4-ml/hour background infusion with a bolus dosage of 4 ml/20 min as needed, and a maximal dosage of 16 ml/h.

## Measurements

A blinded observer evaluated the patients. The primary outcome was pain scores as measured using a numerical rating scale (NRS) (0–10 cm: 0, no pain; 10, worst pain imaginable): NRS pain scores at rest (NRS-R), NRS pain scores during movement (NRS-M), and NRS pain scores when massaging the uterus (NRS-U) (Nie et al., 2017) at 6 and 24 h after skin closure. Overall patient satisfaction scores (0–10: 0, dissatisfied; 10, very satisfied) (Tonosu et al., 2020) were recorded 24 h. Sedation was assessed using the Ramsay Sedation Scale: 1, anxious and restless or agitated or both; 2, cooperative, tranquil, and oriented; 3, somnolent, responds to commands only; 4, asleep, shows brisk response to loud auditory stimulus or light glabellar tap; 5, asleep, shows sluggish response to loud auditory stimulus or light glabellar tap; and 6, asleep, shows no response to loud auditory stimulus or light glabellar tap (Nie et al., 2017). The time of first ambulation (able to walk with help) and the time of first flatus were recorded. If the patient persisted with pain, flurbiprofen axetil (Beijing Tide pharmaceutical, Beijing, China) was intravenously injected and documented. We surveilled for ADRs including pruritus, nausea and vomiting, numbness, headache, and dizziness. We also recorded any hypotension (20% below

baseline blood pressure, baseline blood pressure was defined as the blood pressure in the preoperative assessment or the usual blood pressure at home) (Siddik-Sayyid et al., 2014; Nie et al., 2017) or respiratory depression (respiratory rate <8 breaths/min).

## Statistical Analysis

In this study, analgesic efficacy was the primary outcome. A power analysis showed that 42 patients in each group would provide 80% of the power needed to detect differences among the four groups.

We performed all statistical analyses with SPSS 25.0 software, and statistical significance was set at  $p = 0.05$  (2-sided). A Shapiro-Wilk test, Q-Q plot, and p-p plot were used to confirm normality for continuous variables. All normally distributed continuous variables are reported as means  $\pm$  SD, and non-normally distributed continuous variables are described as medians (25–75% interquartile range [IQR]). One-way ANOVA or Kruskal-Wallis methods were used to compare the differences between/among groups, and Tukey's and Dscf tests were used to perform the post-hoc analyses. The Chi-squared test was used to compare the differences between categorical variables, and data are expressed as N (%) patients.

## RESULTS

Of the 303 patients screened for eligibility, we enrolled 240 patients, and 42 patients were excluded prior to randomization

**TABLE 1** | Patient characteristics and surgical data.

|   | <b>R<sub>1</sub> (43)</b> | <b>R<sub>2</sub> (45)</b> | <b>R<sub>1</sub>S (43)</b> | <b>R<sub>2</sub>S (43)</b> | <b>p values</b> |
|---|---------------------------|---------------------------|----------------------------|----------------------------|-----------------|
| Age (years)                               | 34.1 ± 4.2                | 34.1 ± 3.7                | 34.4 ± 4.1                 | 35.3 ± 4.6                 | 0.445           |
| Height (cm)                               | 162.9 ± 4.9               | 161.6 ± 4.9               | 161.3 ± 6.0                | 162.0 ± 6.0                | 0.536           |
| Weight (kg)                               | 79.0 ± 12.9               | 74.3 ± 10.4               | 76.3 ± 13.9                | 76.8 ± 10.5                | 0.341           |
| Gestational age at delivery (weeks)       | 38 (37–39)                | 38 (38–39)                | 38 (38–38)                 | 38 (38–39)                 | 0.191           |
| Parity (number)                           |                           |                           |                            |                            | 0.645           |
| 1   | 26 (26.0%)                | 29 (29.0%)                | 24 (24.0%)                 | 21 (21.0%)                 |                 |
| 2   | 17 (24.6%)                | 15 (21.7%)                | 17 (24.6%)                 | 20 (29.1%)                 |                 |
| 3   | 0 (0.00%)                 | 1 (20.0%)                 | 2 (40.0%)                  | 2 (40.0%)                  |                 |
| Duration of surgery (min)                 | 44 (38–52)                | 39 (32–43)                | 41 (36–55)                 | 40 (34–49)                 | 0.071           |
| I V infusion volume (ml)                  | 800 (800–900)             | 800 (700–800)             | 800 (700–1,100)            | 800 (700–900)              | 0.543           |
| Estimated blood loss (ml)                 | 300 (200–300)             | 200 (200–300)             | 200 (200–400)              | 200 (200–300)              | 0.859           |
| Puncture interspace location              |                           |                           |                            |                            | 0.685           |
| L3–4                                      | 6 (21.4%)                 | 9 (32.1%)                 | 5 (17.9%)                  | 8 (28.6%)                  |                 |
| L2–3                                      | 37 (25.3%)                | 36 (24.7%)                | 38 (26.0%)                 | 35 (24.0%)                 |                 |
| Dose of intrathecal 0.5% bupivacaine (mg) | 1.5 (1.5–1.6)             | 1.5 (1.5–1.6)             | 1.5 (1.5–1.6)              | 1.5 (1.5–1.6)              | 0.953           |

R<sub>1</sub> group, 0.1% ropivacaine; R<sub>2</sub> group, 0.15% ropivacaine; R<sub>1</sub>S group, 0.1% ropivacaine +0.5 µg/ml of sufentanil; R<sub>2</sub>S group, 0.15% ropivacaine +0.5 µg/ml of sufentanil. Data are expressed as means ± SD, medians (25–75% IQR) or N (%) patients.

(**Figure 1**). One hundred and ninety-eight patients were subsequently randomly allocated to four groups. After randomization, 24 patients were excluded (**Figure 1**). We ultimately analyzed 43 patients in the R<sub>1</sub> group, 45 in the R<sub>2</sub> group, 43 in the R<sub>1</sub>S group, and 43 in the R<sub>2</sub>S group (**Figure 1**).

## Patient Demographics and Surgical Characteristics

Baseline characteristics for the four groups are shown in **Table 1**. There were no statistically significant differences among the four groups with respect to age, height, weight, gestational age at delivery, parity, the duration of surgery, infusion volume, estimated blood loss, the puncture interspace location, or the dose of intrathecal 0.5% hypobaric bupivacaine (all  $p > 0.05$ ).

## Postoperative NRS Scores

Six hours after skin closure, NRS-R scores in the R<sub>1</sub>S (3 [2–3]) and R<sub>2</sub>S (2 [1–3]) groups were lower than those in either the R<sub>1</sub> (3 [3–4]) ( $p < 0.05$ ,  $p < 0.001$ , respectively) or R<sub>2</sub> groups (3 [2–4]) ( $p < 0.05$ ,  $p < 0.01$ , respectively). At 24 h after skin closure, there were no statistically significant differences in NRS-R scores among the four groups ( $p > 0.05$ ) (**Figure 2A**).

We noted that at 6 h after skin closure, NRS-M scores in the R<sub>1</sub>S group (4 [3–5]) were lower than those in the R<sub>2</sub> group (5 [4–6]) ( $p < 0.05$ ), and NRS-M scores in the R<sub>2</sub>S group (4 [3–5]) were lower than in the R<sub>1</sub> (5 [4–6]) ( $p < 0.05$ ) and R<sub>2</sub> (5 [4–6]) ( $p < 0.01$ ) groups. By 24 h after CS, there were no longer any statistically significant differences in NRS-M scores among the four groups ( $p > 0.05$ ) (**Figure 2B**).

By 6 h after skin closure, NRS-U scores in the R<sub>2</sub>S group (6 [5–6]) were lower than those in the R<sub>1</sub> group (7 [6–8]) ( $p < 0.01$ ), but there was no statistically significant differences between R<sub>1</sub>S and R<sub>1</sub> groups ( $p > 0.05$ ). By 24 h after CS, there were no statistically significant differences in scores among the four groups ( $p > 0.05$ ) (**Figure 2C**).

## Patient Satisfaction

Patient satisfaction scores were significantly higher in the R<sub>2</sub>S group (9 [8–10]) relative to the R<sub>1</sub> group (8 [6–8]) ( $p < 0.01$ ). There were no statistically significant differences between any of other two groups (all  $p > 0.05$ ) (**Figure 3**).

## Gastrointestinal Function

The time to patient's first flatus was shorter in the R<sub>2</sub>S group (18.7 ± 11.8 h) compared to the R<sub>1</sub> group (25.9 ± 12.0 h) ( $p < 0.05$ ) (**Figure 4**).

## Requirements for Concomitant Analgesics

The number of self-administered doses of the patient-controlled analgesia (PCA) in the R<sub>2</sub>S group (0 [0–2]) was less than in the R<sub>1</sub> (1 [0–3]) ( $p < 0.05$ ) and R<sub>2</sub> groups (1 [0–4]) ( $p < 0.05$ ), and that was less in the R<sub>1</sub>S group (0 [0–2]) than in the R<sub>2</sub> group (1 [0–4]) ( $p < 0.05$ ) at 6 h, while there were no statistically significant differences among the groups at 24 h ( $p > 0.05$ ). There were no statistically significant differences among the groups regarding the time when highest pain scores were recorded ( $p > 0.05$ ) or the number of patients who requested supplementary analgesia, either at 6 or 24 h (all  $p > 0.05$ ) (**Table 2**).

## Recovery of Motor Function

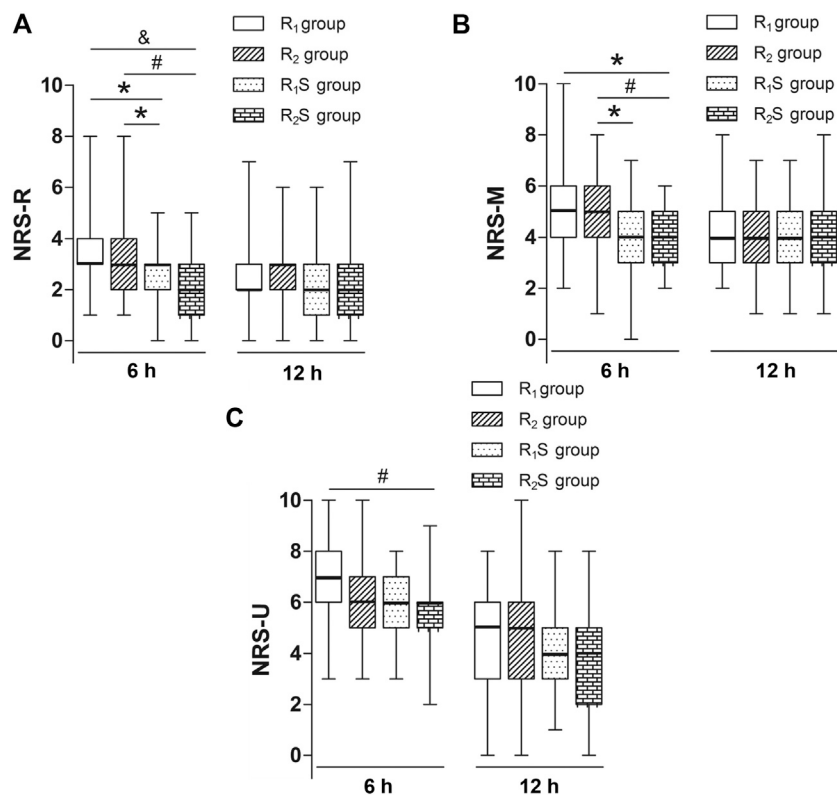
The time to patient's first ambulation was shorter in the R<sub>2</sub>S group (24.8 [22.5–27.5 h]) than in the R<sub>1</sub>S group (27.3 [25.0–28.5 h]) ( $p < 0.05$ ). There were no statistically significant differences between any of other two groups (all  $p > 0.05$ ) (**Table 2**).

## Sedation Scores

We observed no statistically significant differences in Ramsay Sedation Scale scores among the four groups ( $p > 0.05$ ) (**Table 2**).

## Adverse Drug Reactions

Patients in the R<sub>1</sub>S group (4 [9.3%]) had a higher incidence of pruritus at 6 h compared to the R<sub>1</sub> (0 [0]) ( $p < 0.05$ ) and R<sub>2</sub> groups (0 [0]) ( $p < 0.05$ ), while patients in the R<sub>2</sub>S group (4 [9.3%])



**FIGURE 2 | (A)** Numerical rating scale of pain scores at rest (NRS-R) at 6 and 24 h after skin closure. **(B)** Numerical rating scale of pain scores during movement (NRS-M) at 6 and 24 h after skin closure. **(C)** Numerical rating scale of pain scores when massaging the uterus (NRS-U) at 6 h and 24 h after skin closure. R<sub>1</sub> group, 0.1% ropivacaine; R<sub>2</sub> group, 0.15% ropivacaine; R<sub>1</sub>S group, 0.1% ropivacaine + 0.5 µg/ml of sufentanil; R<sub>2</sub>S group, 0.15% ropivacaine + 0.5 µg/ml of sufentanil. Data are expressed as medians (25–75% IQR). \* $p < 0.05$ , # $p < 0.01$ , & $p < 0.001$ .

exhibited a higher incidence of pruritus at 6 h compared to the R<sub>2</sub> group (0 [0] ( $p < 0.05$ )). The incidence of numbness in the R<sub>2</sub> (22 [48.9%],  $p < 0.05$ ; 22 [48.9%],  $p < 0.05$ ) and R<sub>2</sub>S groups (23 [53.5%],  $p < 0.01$ ; 23 [53.5%],  $p < 0.01$ ) was greater than in the R<sub>1</sub> group (10 [23.3%], 10 [23.3%]) at both 6 and 24 h. There were no statistically significant differences among the groups regarding other ADRs, including nausea and vomiting, headache, dizziness, hypotension, or respiratory depression (all  $p > 0.05$ ) (Table 3).

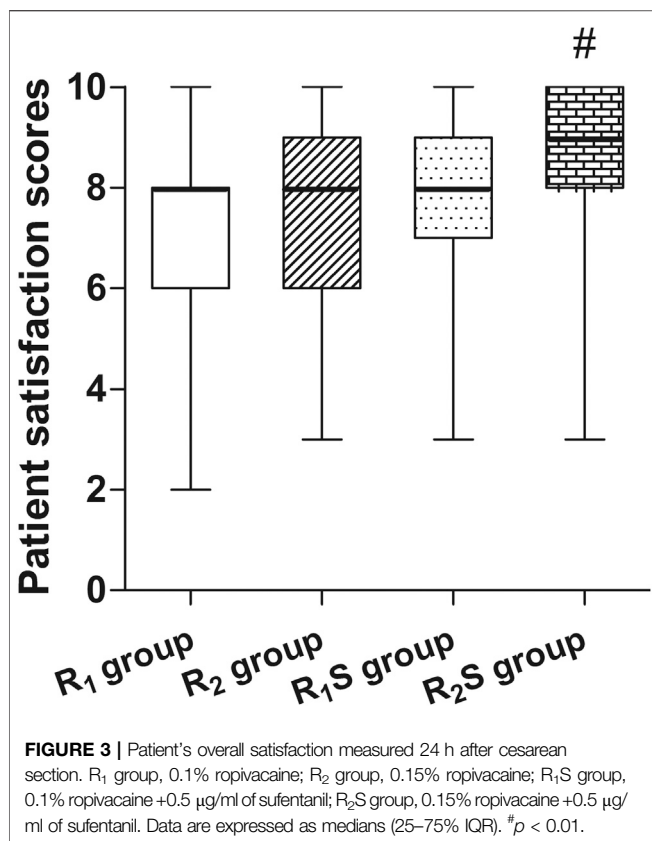
## DISCUSSION

Postoperative analgesia after CS is challenging since we need not only to consider maternal comfort, but the anesthetic technique should also have no ADRs on the newborn. Epidural morphine is commonly used for analgesia after CS (Carvalho and Butwick, 2017), but there is a concomitantly higher incidence of pruritus, nausea and vomiting (Youssef et al., 2014). As these ADRs diminish overall patient satisfaction, we advocate the use of low concentrations of local anesthetics with other opioids so as to reduce opioid dosage and thereby decrease the incidence of ADRs.

The present study indicated that co-administration 0.15% ropivacaine with 0.5 µg/ml of sufentanil epidurally alleviated CS pain at rest, during movement, and when massaging the

uterus, and it reduced the number of self-administered doses of the PCA compared to 0.1% ropivacaine or 0.15% ropivacaine at 6 h. Moreover, it improved overall patient satisfaction scores and reduced the time to first flatus compared to 0.1% ropivacaine. The time to first ambulation was not delayed. However, co-administered with sufentanil increased the incidence of pruritus compared to ropivacaine only at 6 h. Higher concentration of ropivacaine increased the incidence of numbness compared to lower concentration at both 6 and 24 h, whether or not it was co-administered with sufentanil. We believe that although a higher incidence of pruritus and numbness was demonstrated, co-administration of 0.15% ropivacaine with 0.5 µg/ml of sufentanil epidurally may be the better choice for pain relief relative to the other groups due to the lower NRS-R, NRS-M, and NRS-U scores, shorter time to first flatus, and higher patient-satisfaction scores.

Published guidelines advocate for fentanyl and sufentanil for epidural analgesia (Plante and Gaiser, 2017). The authors of a systematic review found that compared with fentanyl, sufentanil was more effective in extending the duration of analgesia when used in CSEA during labor (Zhi et al., 2020). Ropivacaine blocks conduction in the sensory and motor nerves, while sufentanil interrupts pain transmission in the dorsal horn. Therefore, adding sufentanil to ropivacaine may synergistically prolong the

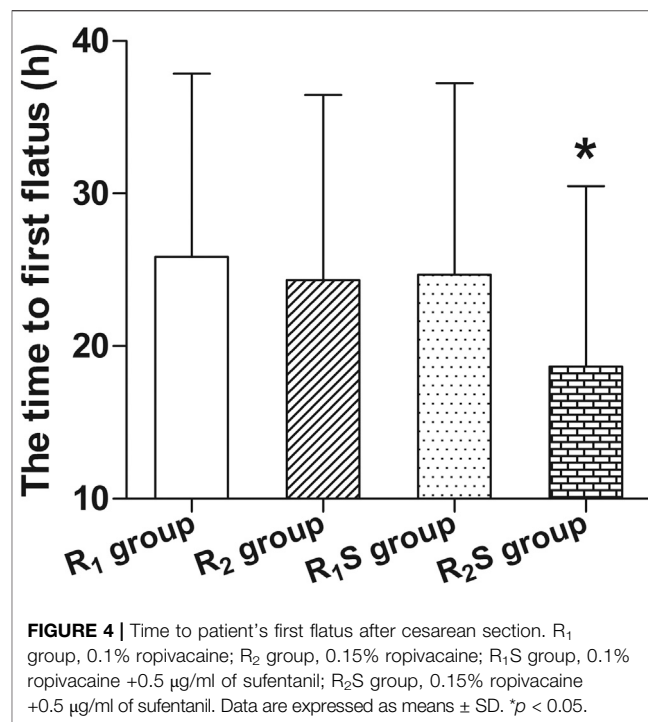


duration of sensory block (Parpaglionni et al., 2009). In the present study, ropivacaine co-administered with sufentanil relieved the pain not only at rest but also during movement compared to ropivacaine only at 6 h. However, when massage the uterus, 0.15% ropivacaine with sufentanil showed an improved analgesic effect, while 0.1% ropivacaine with sufentanil did not show improvement compared with 0.1% ropivacaine only at 6 h. All these results indicated that a higher concentration of ropivacaine (0.15%) with sufentanil produced a stronger analgesic effect.

Although NRS scores were significantly lower in the R<sub>2</sub>S group relative to the other groups, the analgesic effect was not satisfactory in any group when massage the uterus. Carvalho et al. found that patients tolerated moderate pain rather than exposing their baby to any possible harmful effects of analgesics (Carvalho et al., 2005), and others found that pain was not the only factor that determined overall patient satisfaction (Schyns-Van Den Berg et al., 2015); these may be reasons for the high overall satisfaction scores we received. In our study, the rare use of supplementary analgesia may be also attributed—at least partially—to the patients' fear of exposing their baby to any possible harmful analgesics (Carvalho et al., 2005).

Postoperative pain increases the secretion of catecholamines, and sympathetic stimulation prevents the release of acetylcholine (Cho et al., 2017), thus inhibiting the recovery of gastrointestinal function; this may be the reason that time to first flatus in the R<sub>1</sub>, R<sub>2</sub>, and R<sub>1</sub>S groups was longer than that in the R<sub>2</sub>S group.

Early movement hastens postpartum recovery (Macones et al., 2019). Epidural analgesia with local anesthetics may delay



ambulation of the mother, but when administered at low concentrations, the probability is small (Chen et al., 2014). In our study, the time to first ambulation in the R<sub>2</sub>S group was shorter than R<sub>1</sub>S group, this maybe attribute to the better analgesic effect in the R<sub>2</sub>S group than in the R<sub>1</sub>S group. The time to first ambulation in the R<sub>2</sub>S group was not delayed compared with the other groups. We attribute this to better analgesic effect and the administration of low-concentration ropivacaine (0.1% or 0.15%). Other investigators also reported similar results, Liu *et al.* found that 0.2% ropivacaine induced a 30% incidence in motor block, but not in those individuals who received 0.05% or 0.1% ropivacaine (Liu et al., 1999).

Complications of neuraxial drugs are the results of drug absorption into the blood circulation or presence in cerebrospinal fluid, or both. The principal ADRs observed in the present study were numbness and pruritus. The incidence of numbness was higher in the R<sub>2</sub> and R<sub>2</sub>S groups when compared with the R<sub>1</sub> group at both 6 h and 24 h, indicating that higher concentration of ropivacaine (0.15%) increased numbness.

The incidence of pruritus was higher in the R<sub>2</sub>S group relative to the R<sub>2</sub> group, and that was higher in the R<sub>1</sub>S group compared to the R<sub>1</sub> and R<sub>2</sub> groups at 6 h. But the incidence of pruritus in the present study was overall low (9.3% and 7.0% at 6 and 24 h, respectively, in the R<sub>2</sub>S group; and 9.3% and 7.0% at 6 and 24 h, respectively, in the R<sub>1</sub>S group). By contrast, the incidence of epidural morphine (2.5 mg)-induced pruritus was 44% (Youssef et al., 2014). Our use of a small effective dose of sufentanil and the addition of ropivacaine might explain the low incidence of pruritus. Cai *et al.* reported that when ropivacaine was combined with sufentanil for labor analgesia, the incidence of pruritus was 3.3% (lower than what we reported herein), which

**TABLE 2 |** Maternal follow-up.

|  | R <sub>1</sub> (43) | R <sub>2</sub> (45) | R <sub>1</sub> S (43) | R <sub>2</sub> S (43)          | p values |
|--|---------------------|---------------------|-----------------------|--------------------------------|----------|
| Time until greatest pain score experienced (h)           | 9.8 ± 5.9           | 9.1 ± 5.6           | 11.0 ± 6.8            | 10.2 ± 7.4                     | 0.618    |
| Number of self-administered doses                        |                     |                     |                       |                                |          |
| 6 h  | 1 (0–3)             | 1 (0–4)             | 0 (0–2) <sup>*3</sup> | 0 (0–2) <sup>*1,2</sup>        | 0.026    |
| 24 h   | 0 (0–2)             | 0 (0–1)             | 0 (0–0)               | 0 (0–1)                        | 0.199    |
| Number of patients who requested supplementary analgesia |                     |                     |                       |                                |          |
| 6 h  | 3 (7.0%)            | 2 (4.4%)            | 4 (9.3%)              | 0 (0)                          | 0.243    |
| 24 h   | 0 (0)               | 0 (0)               | 1 (2.3%)              | 0 (0)                          | 0.382    |
| Time to first ambulation (h)                             | 25.3 (23.7–28.0)    | 26.7 (24.6–28.1)    | 27.3 (25.0–28.5)      | 24.8 (22.5–27.5) <sup>*4</sup> | 0.019    |
| Ramsay sedation scale scores                             |                     |                     |                       |                                |          |
| 6 h  |                     |                     |                       |                                | 0.371    |
| 1  | 3 (7.0%)            | 2 (4.4%)            | 0 (0)                 | 1 (2.3%)                       |          |
| 2  | 40 (93.0%)          | 43 (95.6%)          | 43 (100%)             | 41 (95.4%)                     |          |
| 3  | 0 (0)               | 0 (0)               | 0 (0)                 | 1 (2.3%)                       |          |
| 4  | 0 (0)               | 0 (0)               | 0 (0)                 | 0 (0)                          |          |
| 5  | 0 (0)               | 0 (0)               | 0 (0)                 | 0 (0)                          |          |
| 6  | 0 (0)               | 0 (0)               | 0 (0)                 | 0 (0)                          |          |
| 24 h   |                     |                     |                       |                                | 0.886    |
| 1  | 3 (7.0%)            | 2 (4.4%)            | 0 (0)                 | 1 (2.3%)                       |          |
| 2  | 40 (93.0%)          | 42 (93.4%)          | 40 (93.0%)            | 41 (95.3%)                     |          |
| 3  | 0 (0)               | 1 (2.2%)            | 1 (2.3%)              | 0 (0)                          |          |
| 4  | 0 (0)               | 0 (0)               | 0 (0)                 | 0 (0)                          |          |
| 5  | 0 (0)               | 0 (0)               | 0 (0)                 | 0 (0)                          |          |
| 6  | 0 (0)               | 0 (0)               | 0 (0)                 | 0 (0)                          |          |

R<sub>1</sub> group, 0.1% ropivacaine; R<sub>2</sub> group, 0.15% ropivacaine; R<sub>1</sub>S group, 0.1% ropivacaine +0.5 µg/ml of sufentanil; R<sub>2</sub>S group, 0.15% ropivacaine +0.5 µg/ml of sufentanil. Data are expressed as means ± SD, medians (25–75% IQR) or N (%) patients. <sup>\*1</sup>p < 0.05: R<sub>2</sub>S group vs. R<sub>1</sub> group, <sup>\*2</sup>p < 0.05: R<sub>2</sub>S group vs. R<sub>2</sub> group, <sup>\*3</sup>p < 0.05: R<sub>1</sub>S group vs. R<sub>2</sub> group, <sup>\*4</sup>p < 0.05: R<sub>1</sub>S group vs. R<sub>2</sub>S group.

**TABLE 3 |** Adverse effects.

|                        | R <sub>1</sub> (43) | R <sub>2</sub> (45)      | R <sub>1</sub> S (43)    | R <sub>2</sub> S (43)    | p values |
|------------------------|---------------------|--------------------------|--------------------------|--------------------------|----------|
| Pruritus               |                     |                          |                          |                          |          |
| 6 h                    | 0 (0)               | 0 (0)                    | 4 (9.3%) <sup>*3,4</sup> | 4 (9.3%) <sup>*2</sup>   | 0.035    |
| 24 h                   | 0 (0)               | 0 (0)                    | 3 (7.0%)                 | 4 (7.0%)                 | 0.095    |
| Numbness               |                     |                          |                          |                          |          |
| 6 h                    | 10 (23.3%)          | 22 (48.9%) <sup>*5</sup> | 17 (39.5%)               | 23 (53.5%) <sup>*1</sup> | 0.023    |
| 24 h                   | 10 (23.3%)          | 22 (48.9%) <sup>*5</sup> | 17 (39.5%)               | 23 (53.5%) <sup>*1</sup> | 0.023    |
| Nausea and vomiting    |                     |                          |                          |                          |          |
| 6 h                    | 1 (2.3%)            | 1 (2.2%)                 | 2 (4.7%)                 | 1 (2.3%)                 | 0.885    |
| 24 h                   | 0 (0)               | 1 (2.2%)                 | 0 (0)                    | 1 (2.3%)                 | 0.577    |
| Headache               |                     |                          |                          |                          |          |
| 6 h                    | 0 (0)               | 1 (2.2%)                 | 0 (0)                    | 0 (0)                    | 0.410    |
| 24 h                   | 1 (2.3%)            | 0 (0)                    | 1 (2.3%)                 | 0 (0)                    | 0.558    |
| Dizziness              |                     |                          |                          |                          |          |
| 6 h                    | 0 (0)               | 1 (2.2%)                 | 1 (2.3%)                 | 1 (2.3%)                 | 0.800    |
| 24 h                   | 0 (0)               | 2 (4.4%)                 | 0 (0)                    | 0 (0)                    | 0.122    |
| Hypotension            |                     |                          |                          |                          |          |
| 6 h                    | 0 (0)               | 0 (0)                    | 0 (0)                    | 1 (2.3%)                 | 0.382    |
| 24 h                   | 0 (0)               | 0 (0)                    | 0 (0)                    | 0 (0)                    | 1.000    |
| Respiratory depression |                     |                          |                          |                          |          |
| 6 h                    | 0 (0)               | 0 (0)                    | 0 (0)                    | 0 (0)                    | 1.000    |
| 24 h                   | 0 (0)               | 0 (0)                    | 0 (0)                    | 0 (0)                    | 1.000    |

R<sub>1</sub> group, 0.1% ropivacaine; R<sub>2</sub> group, 0.15% ropivacaine; R<sub>1</sub>S group, 0.1% ropivacaine +0.5 µg/ml of sufentanil; R<sub>2</sub>S group, 0.15% ropivacaine +0.5 µg/ml of sufentanil. Data are expressed as N (%) patients. <sup>\*1</sup>p < 0.01: R<sub>2</sub>S group vs. R<sub>1</sub> group; <sup>\*2</sup>p < 0.05: R<sub>2</sub>S group vs. R<sub>2</sub> group; <sup>\*3</sup>p < 0.05: R<sub>1</sub>S group vs. R<sub>1</sub> group; <sup>\*4</sup>p < 0.05: R<sub>1</sub>S group vs. R<sub>2</sub> group; <sup>\*5</sup>p < 0.05: R<sub>2</sub> group vs. R<sub>1</sub> group.

may be due to the lower concentration of sufentanil (0.3 µg/ml) the authors used (Cai et al., 2020). Pruritus may, at times, be more unpleasant for patients than pain, from this perspective, epidural sufentanil appears to be better than morphine.

With respect to other ADRs such as nausea and vomiting, headache, dizziness, hypotension, and respiratory depression, there were no significant differences among the four groups.

There were some limitations to our study. First, we did not assess the possible preoperative confounding factors for pain after CS (Pan et al., 2013). However, the previous pain experience due to a preceding CS was evenly distributed among the four groups. Second, the observation period was the initial 24 h, and we recommend that future studies lengthen the observation time to 48 h or even longer. Third, in the present study, the incidence of urinary retention was not recorded, as the urinary catheter was inserted prior to surgery and removed after patients could walk with assistance in the ward.

## CONCLUSIONS

Although the ADRs (pruritus and numbness) were greater in the R<sub>2</sub>S group, by significantly reducing the pain scores and the time to first flatus, patients reported higher satisfaction scores in the R<sub>2</sub>S group relative to other groups. In conclusion, the epidural co-administration of 0.15% ropivacaine and 0.5 µg/ml of sufentanil (at a 4 ml/h background infusion with a bolus dosage of 4 ml/20 min as needed) may be the better choice for post-cesarean analgesia compared to the other three regimens investigated in this study.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Xuanwu Hospital of Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

F-FM, YL, and T-LW designed the project; K-PF performed the spinal-epidural anesthesia; R-XH monitored the patients; Q-FD observed the patients; F-FM and X-XF analyzed the data; F-FM

and DJ wrote the manuscript; LF and T-LW revised the manuscript. All authors approved the final version of the manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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