Comparison Between the Use of Ropivacaine Alone and Ropivacaine With Sufentanil in Epidural Labor Analgesia

Xian Wang, MD, MSc, Shiqin Xu, MD, MPH, Xiang Qin, MD, Xiaohong Li, MD, Shan-Wu Feng, MD, PhD, Yusheng Liu, MD, MSc, Wei Wang, MD, MSc, Xirong Guo, MD, PhD, Rong Shen, MD, Xiaofeng Shen, MD, MPH, and Fuzhou Wang, MD, PhD

Abstract: To compare the analgesic efficacy and safety of the sole local anesthetic ropivacaine with the combination of both local anesthetic ropivacaine and opioidergic analgesic sufentanil given epidurally on the labor pain control. After institutional review board approval and patient consent, a total of 500 nulliparas requesting epidural labor analgesia were enrolled and 481 eventually were randomized into 2 groups: a sole local anesthetic group (ropivacaine 0.125%) and a combination of local anesthetic and opioidergic analgesic sufentanil given epidurally in a single bolus, followed by intermittent bolus injection of 10 to 15 mL of the solution. The primary outcome was the analgesic efficacy measured using Numerical Rating Scale (NRS) of pain. Other maternal and infant variables were evaluated as secondary outcomes. A total of 346 participants completed the study. The median NRS pain score during the 1st stage of labor was significantly lower in the combination group 2.2 (interquartile range [IQR]: 1.8–2.7) comparing to the sole local analgesic group 2.4 (IQR: 2.0–2.8) ($P < 0.0001$). No significant difference was observed in NRS pain score prior epidural analgesia and during the 2nd stage of labor. Patients in both groups rated same satisfaction of analgesia. Patients in the sole local analgesic group experienced fewer side effects than those in the combination group (37.7% vs 47.2%, $P = 0.082$). The individual analgesia-related cost in the sole local analgesic group was less ($5.7 \pm 2.06$) than that in the combination group ($9.76 \pm 3.54$) ($P < 0.0001$). The incidence of 1-minute Apgar $\leq 7$ was lower in the sole local analgesic group 2.4 (1.2%) than the combination group 10.5% ($P = 0.038$). No difference was found between other secondary outcomes.

The sole local anesthetic ropivacaine produces a comparable labor analgesic effect as the combination of both local anesthetic ropivacaine and opioidergic analgesic sufentanil at different stages of labor ($\Delta_{NRS} = 0.2$) but the former has less side effects, lower cost, and less incidence of lower 1-minute Apgar scoring. These results imply the necessity of a systematic reevaluation of epidural labor analgesia with sole local anesthetics against combination regimens of local anesthetics and other opioids.

(Medicine 94(43):e1882)

INTRODUCTION

Labor pain has been considered as 1 of the most unbearable pain, and a number of medical procedures have been introduced for relieving it. Epidural analgesia is the most effective procedure over other techniques. Currently available epidural analgesic regimen recommends adding opioids into local anesthetics to provide superior analgesia through sparing local anesthetics and prolonging the analgesic duration over the single shot intrathecal or intermittent epidural bolus technique of labor pain control. The duration of action is of little concern when patient-controlled epidural analgesia is used for labor, and the benefits of local anesthetic-sparing effects induced by opioids must be weighed against opioid-associated acute and long-term side effects for both mothers and neonates. Except for acute side effects such as nausea, vomiting, pruritus, and urinary retention, epidural opioid has been reported to be associated with lower breast-feeding success rate at 6 weeks postpartum, rise in maternal temperature during labor, fetal bradycardia, neonatal respiratory depression, and alterations in neonatal neurobehavior, and overly poor outcomes in newborns. As early as 1980s, Golub and colleagues had paid attention to the disposition of intrapartum narcotic analgesics and its long-term influence on neonatal behaviors in monkeys. The use of preemptive morphine analgesia in neonatal intensive care unit was associated with injury of the long-term neurocognitive, behavioral, and adaptive outcomes in early childhood. In sum, opioid must be used with caution for epidural labor analgesia.
Ahirwar et al observed that sole ropivacaine was effective in decreasing labor pain without any motor blockade compared with a combination of ropivacaine with fentanyl or clonidine. Moreover, when comparing epidural fentanyl only or fentanyl supplemented with bupivacaine during the 2nd stage for labor, no significantly difference was found with regard to delivery method, labor pain control, maternal or neonatal outcomes, as well as the time of the 2nd stage of labor. Our previous study observed the analgesic effect of epidural ropivacaine plus sufentanil for labor, and this analgesic soup effectively relieved labor pain without significant delay of the labor progression. However, in a recently published meta-analysis, fentanyl and sufentanil in combination with bupivacaine have been found to provide comparable analgesic properties via the epidural or intrathecal routes for labor pain relief, but the number of neonates with Apgar ≤ 7 was significantly greater in bupivacaine and sufentanil treated women. As thus, we designed this randomized controlled trial to test the hypothesis that sole ropivacaine would produce similar analgesic effect as the combination of ropivacaine with sufentanil but with fewer side effects and superior neonatal outcomes.

MATERIALS AND METHODS

Subjects and Ethics

After the institutional review board approval, primiparous women with a single, live, term fetus, as well as requesting epidural labor analgesia were questioned to participate in the study immediately after entering into the delivery room. All of the eligible parturients signed an individual informed consent. With the analgesia, each parturient was given a detailed interpretation of the epidural puncture and catheterization, analgesics used for epidural analgesia, possible accidentals such as failed epidural catheterization and inadvertent epidural puncture, and alternative rescues that would be provided as well. The study was conducted between January 2014 and June 2014 at a tertiary university hospital in China. The rate of epidural labor analgesia is as high as 95% in our institution during the experimental period.

Exclusion Criteria

Participants with 1 or more of the following indications were excluded from the trial: twin gestation; multiparous women; ≤18 yr or ≥ 45 yr; failed epidural catheterization or inadvertent epidural puncture; dependent or allergic to opioidergic analgesics; concurrent with pregnancy-induced diabetes mellitus and hypertension; data collected incompletely; retreated from the study; group assignment violation; and lost to follow-up.

For those who did not request epidural analgesia were not included into the study; but alternative pain relieving methods such as the intravenous or intramuscular analgesia were still available to them. Even the epidural labor analgesia could be requested post the eligibility-checking period, and it still would be provided by the anesthesiologist on duty; however, the corresponding data were not included in this study. Meanwhile, all of the parturients with epidural analgesia or not were all treated with standard obstetric procedures (detailed procedures can be found in our previous work).

Randomization Assignment

After initial screening, eligible subjects were assigned to either the sole local anesthetic group or the combination group through a randomization allocation protocol with the random number generated via the online software QuickCalc® (GraphPad, San Diego, CA). Numbers with regard to the study group assignment were sealed and kept by 1 nonstudy member. Immediately after epidural labor analgesia requested by the parturient, the group assignment number allocated to determine which analgesic medication would be given was disclosed. Except for the parturients and caregivers, the data-collecting and data-analyzing members were blinded to the group assignment.

Demographic Characteristics

In this study, we collected following demographic characteristics: gestational age of fetus, age at delivery, height and weight of the parturient, smoking or not, education experience, history of surgical operation, history of chronic pain, and depression.

Analgesia Protocol

After initial screening, enrolled participants were randomized into 1 of the 2 groups through the above-mentioned premade random-number table: sole local anesthetic group (epidural ropivacaine only) and the local anesthetic + opioid group (epidural ropivacaine combined with sufentanil) (Figure 1). First and second stages of labor in this study were defined according to the guidelines from the National Institute for Health and Clinical Excellence. Upon subject’s request for epidural analgesia and post-signature of informed contents, epidural puncture and catheterization were implemented by the anesthesiologist on duty. The analgesic compositions for epidural medication were as follows: Initially, 45 mg of lidocaine (1.5%) in 3.0 mL containing 5 μg/mL epinephrine was injected epidurally to all parturients as a test dose. Then, a bolus of 10 mL epidural analgesic with only 1.25 mg/mL (0.125%) ropivacaine or 1.25 mg/mL ropivacaine in combination with 0.3 μg/mL sufentanil was given in the respective groups of the sole local analgesic or the combination analgesia. For the concentration of sufentanil, we used 0.3 μg/mL as our institutional reference presented in our previous study. After the single bolus, an epidural pump with patient-control buttons was connected, the pump parameters were set up as follows: no background infusion, a 10 to 15 mL patient-controlled bolus depending on patient’s height, the hourly volume limit of 30 mL, and the lockout interval of 15 minutes. If epidural catheterization failed or accidental epidural puncture happened during performing epidural procedures, alternative analgesia was provided, and standard therapeutic procedures were followed, these parturients were excluded from per protocol (PP) analysis, but included in the intention-to-treat (ITT) analysis.

Peripartum Monitor and Management

Before the implementation of epidural labor analgesia, a left or right antecubital vein was catheterized for infusing fluid or drugs. A total of 8 mL/kg of Ringer’s solution was administered to supplement the pre-existing fluid deficits and maintenance requirements 15 minutes before the beginning of the epidural medication. Hemodynamic variables, urine output, and the hemoglobin concentration were also monitored to guide the intrapartum fluid management. According to the standard obstetric indications, oxytocin was titrated by the obstetricians in some parturients. Besides, instrumental vaginal delivery or mediolateral episiotomy was
decided and performed by the obstetricians following the maternal, neonatal, or/and obstetric indications. In our institute, the practice of all caregivers including obstetric staffs was standardized under the condition of with or without epidural labor analgesia.

The patient’s perception of labor pain was rated from prior analgesia to the ends of the 1st and 2nd stages based on a Numerical Rating Scale (NRS) scoring system (0–10 linear gauge, 0: no pain, 10: worst imaginable pain). Besides, the maternal analgesia satisfaction with the 1st stage, the 2nd stage, and the overall delivery as well was assessed using the Visual Analog Scale (VAS; a 0–10 linear gauge, 0: dissatisfactory, 10: very satisfactory).

**Fetal and Neonatal Treatment**

External electronic fetal heart rate was continuously monitored and tocodynamometry was applied to all parturients. One- and 5-minute neonatal Apgar scorings were evaluated by the pediatricians. Meanwhile, umbilical cord artery blood gas analysis was measured and recorded.

**Primary Outcome**

The primary outcome was the analgesic efficacy measured using NRS pain score.

**Secondary Outcomes**

In this study, we selected following variables as the secondary outcomes: maternal VAS analgesia satisfaction at the end of the different stages of labor; intrapartum epidural analgesia-related maternal side effects and modified Bromage scale (0–3); neonatal outcomes including Apgar scorings and umbilical-cord blood gas. Meanwhile, drug consumption and analgesia-associated cost were also evaluated. The method of delivery, that is, the rates of Cesarean and instrumental vaginal delivery; perineal trauma including mediolateral episiotomy and laceration, and successful breastfeeding at postpartum 6 weeks were also recorded.

**Sample Size Calculation**

In this study, we calculated the sample size according to patient’s self-reported NRS scorings due to the pain score was the primary outcome. In a prior study from which the power table where $\delta$ (the mean difference in NRS pain score) was established. The overall patient-reported NRS pain scoring in our institution is 3.24, which was regarded as the reference, when ropivacaine was given in combination with sufentanil. In comparison, our pilot study measured 3.53 of NRS pain score when single ropivacaine was given, and the standard deviation (SD) of the sampled patients was 1.29. When $\alpha$ was set at 0.05, $\beta$ at 0.10, and the power of test ($1 - \beta$) at 0.90, a minimum of 207 subjects per group was needed to detect above difference statistically. To account for the potential dropouts or missing data, the sample size was increased to 250 in each group. A 21% increase in sample size in this trial was mainly based on our previous labor pain-associated clinical trials in which the average dropping out rate was 17% (interquartile range, IQR 11–21%). Therefore, the sample size was increased to 250 in each group by the upper limit 21%.

**Statistical Analysis**

The dropout cases and excluded ones after randomization were analyzed on the ITT basis. All the participants who successfully completed the study were analyzed through the PP manner.

Statistical analyses were done using GraphPad Prism v.5.0 (GraphPad) or SPSS v.13.0 software (SPSS, Inc., Chicago, IL). A value of $P < 0.05$ was considered to be statistically significant. Data are presented as the mean (SD), median (IQR), or number (percentage). Categorical variables were analyzed using the Chi-squared test. Parametric variables were compared with the Student $t$ test. Non-normally distributed variables
including patient’s self-rated NRS scores of pain, VAS scales of analgesia satisfaction, and modified Bromage scale were analyzed through Mann–Whitney U test. Different time lengths of various stages of labor were estimated with the Kaplan–Meier curves, and difference between the groups was compared with the log-rank test as described previously.14

RESULTS

A total of 500 subjects were screened for eligibility. Nineteen parturients were excluded during the screening period due to the reasons shown in the flowchart (Figure 1). Eventually, 481 subjects were randomly assigned to the 2 groups with 241 subjects in the sole local analgesic group and 240 subjects in the combination group. There were 77 and 63 participants in the sole local analgesic group and combination group, respectively, and such a difference in pain score did not make a substantial difference of the satisfaction upon the analgesia using the VAS regimen, that is, 10 (10–10) versus 10 (10–10) (P = 0.742; 0.459).

Table 1 summarizes the demographic characteristics and medical history of the enrolled patients, and they were comparable between the 2 groups. The initial cervical dilation in both groups was similar (Table 2). As the primary outcome, the average NRS pain scores during different stages of labor were evaluated (Table 2). The NRS pain scores in the combination group was significantly lower than the sole local analgesic group during the 1st stage of labor (P < 0.0001), but the mean difference (Δ) between the 2 groups was approximately 0.23. And such a difference in pain score did not make a substantial difference of the satisfaction upon the analgesia using the VAS regimen, that is, 10 (10–10) versus 10 (10–10) (P = 0.742; 0.459).

TABLE 1. Demographic Characteristics of the Patients

|                | Sole Local Anesthesia (n = 164) | Local Anesthesia + Opiod (n = 182) |
|----------------|---------------------------------|------------------------------------|
| Age, yr        | 28.2±2.8                        | 28.1±2.7                           |
| Height, cm     | 162.8±4.9                       | 162.5±4.1                          |
| Weight, kg     | 70.6±8.5                        | 70.5±8.3                           |
| Gestational age, wk | 39.5±1.1                | 39.6±0.9                           |
| Smoking, n (%) | 1 (0.6)                         | 2 (1.1)                            |
| Education, n (%) |                  |                                    |
| <9 yr          | 4 (2.4)                         | 9 (4.9)                            |
| 9–15 yr        | 63 (38.4)                       | 60 (32.9)                          |
| >15 yr         | 97 (59.1)                       | 113 (62.1)                         |
| Surgical history, n (%) | 46 (28)                | 51 (28)                            |
| Chronic pain, n (%) | 9 (5.5)                 | 11 (6)                             |
| Depression, n (%) | 1 (0.6)                  | 0 (0)                              |

Table 2. Analgesia and Associated Variables

|                | Sole Local Anesthesia (n = 164) | Local Anesthesia + Opiod (n = 182) | P Value |
|----------------|---------------------------------|------------------------------------|---------|
| Initial cervix, cm | 1.9±0.5                     | 1.8±0.5                            | 0.3     |
| Pain scorings (NRS, 0–10) |                  |                                    |         |
| Prior analgesia, mean ± SD | 9.2±0.8                | 9.1±0.9                            | 0.893   |
| Prior analgesia, median (IQR) | 9.1 (8.2–10.0)          | 9.1 (8.4–10.0)                     | 0.97    |
| 1st stage, mean ± SD | 2.4±0.5                    | 2.3±0.8                            |<0.0001 |
| 1st stage, median (IQR) | 2.4 (2.0–2.8)            | 2.2 (1.8–2.7)                      |<0.0001 |
| 2nd stage, mean ± SD | 4.5±2.8                    | 4.2±1.2                            | 0.103   |
| 2nd stage, median (IQR) | 4 (4–5)                  | 4 (4–5)                            | 0.104   |
| Drug consumption |              |                                    |         |
| Ropivacaine, mg | 38.6±12.8                   | 37.5±13.5                          | 0.602   |
| Sufentanil, μg | —                            | 12.0±4.3                           | —       |
| Analgesia at the 2nd stage, n (%) | 70 (42.6)                | 78 (42.8)                          | 0.974   |
| Analgesia onset of the 1st analgesic bolus, min | 10.2±3.1             | 9.8±3.7                            | 0.419   |
| Analgesia duration of the 1st analgesic bolus, min | 117.4±29.9           | 124.0±36.2                         | 0.004   |
| Modified Bromage scale (0–3) | 0 (0–0)               | 0 (0–0)                            | —       |
| Ephedrine administration, n (%) | 0 (0)                   | 0 (0)                              | —       |
| Atropine administration, n (%) | 0 (0)                  | 0 (0)                              | —       |
| Lateralized analgesia, n (%) | 5 (3.0)                 | 1 (0.5)                            | 0.08    |
| Labor progression, median (IQR) |        |                                    |         |
| 1st stage, min | 480 (330–568)               | 480 (360–570)                       | 0.741   |
| 2nd stage, min | 33 (25–48)                 | 36 (28–47)                          | 0.463   |
| 3rd stage, min | 9 (7–10)                   | 9 (7–10)                           | 0.533   |
| Total volume of blood, mL | 266.6±34.7           | 263.3±51.6                         | 0.418   |
| Total transfusion of fluid, mL | 562.6±160.8          | 557.7±152.5                        | 0.996   |
| Analgesia satisfaction (VAS, 0–10), median (IQR) |        |                                    |         |
| 1st stage | 10 (10–10)                 | 10 (10–10)                         | 0.742   |
| 2nd stage | 10 (9–10)                  | 10 (9–10)                          | 0.434   |
| Overall | 10 (9–10)                  | 10 (9–10)                          | 0.459   |

IQR = interquartile range, NRS = Numerical Rating Scale, SD = standard deviation, VAS = Visual Analog Scale. Bold emphasized values indicate statistically significant when P was set at < 0.05.
Table 2). Other than pain score, the duration of analgesia after bolus injection was recorded. We found that a single bolus of ropivacaine plus sufentanil produced longer (124.0 ± 36.2 minutes) duration than the sole ropivacaine (117.4 ± 29.9 minutes; P = 0.004). However, the analgesia onset in both groups was similar, 10.2 ± 3.1 versus 9.8 ± 3.7 minutes (P = 0.419).

Although no significant difference was detected in the side effects between the 2 groups, the total number of patients in the sole local analgesic group experienced less side effects than those in the combination group (37.7% vs 47.2%, P = 0.082) (Table 3). This still concerned us that sufentanil addition into ropivacaine causes more side effects even though the difference cannot be detected statistically.

The duration of postanalgesia oxytocin administration in the sole local analgesic group was significantly longer than those of combination group, 4.4 ± 1.8 versus 3.9 ± 1.5 hr (P = 0.029; Table 4). The individual analgesia-related drug cost in the sole local analgesic group was significantly lower than that in the combination group, $5.7 ± 2.06 versus $9.76 ± 3.54 (P < 0.0001; Table 4). For other secondary maternal outcomes like delivery methods, perineal laceration, and breastfeeding, etc., we did not find marked difference between the 2 groups (Table 4).

The 1-minute Apgar scoring was 10 (7–10) versus 10 (6–10) in the sole local analgesic group and combination group, respectively (P = 0.006), and the total neonates with a 1-minute Apgar ≤ 7 were 2 (1.2%) in the local analgesic group and 10 (5.5%) in the combination group (P = 0.038; Table 5).

Figure 2 shows the time durations of different labor stages in Kaplan–Meier curves, and no difference was observed between the 2 groups in all of the stages of labor.

**DISCUSSION**

The data from our study indicated that sole ropivacaine produced a comparable analgesic effect as the combination of both ropivacaine and sufentanil for labor analgesia. Besides, sole epidural ropivacaine was associated with fewer side effects, less incidence of neonatal lower 1-minute Apgar scoring, and lower analgesia-related cost. This study warranted us to reconsider the rationality of supplementing opioidergic analgesics with local anaesthetics for labor analgesia.

The efficacy and safety of ropivacaine in combination of sufentanil for labor pain control had been demonstrated by numerous studies. In our study, the combination of 0.125% ropivacaine with 0.3 μg/mL sufentanil produced a statistically analgesic advantage over the sole 0.125% ropivacaine as demonstrated by a lower NRS pain score during the 1st stage of labor. However, the mean difference (ΔNRS = 0.23) between the 2 groups are comparable clinically majorly because of 2 reasons: patients in both groups reported their pain <2.5, which are within the endurable scale (NRS ≤ 3.0)20,21; and given the excellent correlation between NRS and VAS of pain,22 over 20 mm decrease in VAS that equals 2.0 decrease in NRS is considered as a meaningful improvement of analgesia.23 So all the patients in the 2 groups experienced more than 70% decrease of their NRS pain score, that is, from 9.1 (median, prior analgesia) to ~2.3 (median, postanalgesia), which was also defined as a substantial improvement of pain intensity (≥50% decrease) by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT).24 Meanwhile, all of the subjects were very satisfactory with labor pain control during the 1st stage of labor using the VAS regimen, 10 (10–10) versus 10 (10–10) in the sole local anesthetic group and the combination group, respectively. Further, during the 2nd stage of labor, both NRS pain score and VAS analgesia satisfaction scale were not statistically different between the 2 groups. Taken together, we suggested that role ropivacaine produced a comparable analgesic effect as the combination of both ropivacaine and sufentanil for labor analgesia in our study.

Although discontinuing epidural analgesia to improve a woman’s ability to push and prevent possible adverse obstetric consequences lacks sufficient evidence support, the practice of discontinuing epidurals late in labor is widespread including our institute.25 Another possibility we think is that women may concentrate on childbirth per se at the 2nd stage rather than press the PECA button to ameliorate the slight pain. Local anesthetics and opioids appear to act synergistically to provide superior analgesia.3,26 It is considered that the addition of sufentanil to ropivacaine may short latency, spare the dose of ropivacaine, and considerably prolong analgesia.27 Indeed, in our study, a combination of sufentanil and ropivacaine has a relative shorter onset time compared with the sole ropivacaine. However, this difference has no statistical significance. Otherwise, the 1st bolus with a combination regimen had a statistically longer duration than the sole ropivacaine. However, this extent of synergy does not reduce the ropivacaine consumption during childbirth with similar labor duration. Combining the sufentanil consumption only in the combination group, the corresponding drug cost in the sole local analgesic group is unexpectedly lower, nearly half of the combination group per person. Therefore, the advantage of the sufentanil-related synergistic effect on ropivacaine usage was limited in the context of labor analgesia.

Compared to an equipotent sensory dose of bupivacaine, ropivacaine may be associated with less potential for cardiovascular toxicity and less motor blockade. A wide range of ropivacaine concentration varying from 0.08% to 0.20% may be applied for epidural labor analgesia, with less motor block when

**TABLE 3.** Advance Events or Side Effects

|                      | Sole Local Anesthesia (n = 164) | Local Anesthesia + Opiod (n = 182) | P Value |
|----------------------|--------------------------------|----------------------------------|---------|
| Intrapartum, n (%)   |                                |                                  |         |
| Pyrexia              | 35 (21.3)                      | 39 (21.4)                        | 0.984   |
| Pruritus             | 0                              | 3 (1.6)                          | 0.098   |
| Drowsiness           | 0                              | 0                                | 0.698   |
| Shivering            | 0                              | 0                                | —       |
| Dizziness            | 0                              | 0                                | —       |
| Nausea               | 0                              | 0                                | —       |
| Vomiting             | 0                              | 0                                | —       |
| Sedation             | 0                              | 0                                | —       |
| Tinnitus             | 0                              | 0                                | —       |
| Fetal heart rate deceleration | 0                             | 4 (2.2)                          | 0.056   |
| Overall              | 35 (21.3)                      | 46 (25.3)                        | 0.388   |
| Postpartum, n (%)    |                                |                                  |         |
| Headache             | 0                              | 1 (0.5)                          | 0.342   |
| Postpartum back pain | 26 (15.8)                      | 38 (20.8)                        | 0.229   |
| Nerve complication   | 1 (0.6)                        | 1 (0.5)                          | 0.941   |
| Fecal incontinence   | 0                              | 0                                | —       |
| Urine incontinence   | 0                              | 0                                | —       |
| Overall              | 27 (16.4)                      | 40 (21.9)                        | 0.195   |
lower than 0.17%. No patients in both groups underwent motor blockade with the ropivacaine concentration of 0.125% evaluated with the modified Bromage scale. Other than the relative lower concentration of local anesthetics used in our study, the cumulative dose of local anesthetics consumption determining the degree of motor block was also comparable in the 2 groups. Further, the mode of patient controlled epidural analgesia (PCEA) self-administered bolus without background infusion used in our study was also been considered to be associated with less anesthetics consumption, which indirectly producing less motor block. As such, either combining sufentanil or not, 0.125% ropivacaine for labor analgesia with PCEA regimen produced no motor block and was safe for ambulation analgesia.

### TABLE 4. Maternal Outcomes

|                          | Sole Local Anesthesia (n = 164) | Local Anesthesia + Opiod (n = 182) | P Value |
|--------------------------|---------------------------------|-----------------------------------|---------|
| Cesarean, n (%)          | 25 (10)                         | 25 (10)                           | 1.0     |
| Instrumental, n (%)      | 2 (1.2)                         | 0 (0)                             | 0.135   |
| Medio-lateral episiotomy, n (%) | 105 (64)                  | 103 (56.5)                        | 0.158   |
| Perineal laceration, n (%) |                                 |                                   |         |
| 1°                       | 36 (21.9)                       | 50 (27.5)                         | 0.235   |
| 2°                       | 21 (12.8)                       | 24 (13.2)                         | 0.916   |
| 3°                       | 0                               | 0                                 | —       |
| 4°                       | 0                               | 0                                 | —       |
| Total                    | 57 (34.7)                       | 74 (40.7)                         | 0.258   |
| Antibiotic administration, hr | 5.7 ± 1.1                    | 5.4 ± 1.4                         | 0.768   |
| Breastfeeding, n (%)     | 163 (99.4)                      | 182 (100)                         | 0.291   |
| 6 wk                     | 163 (99.4)                      | 181 (99.5)                        | 0.941   |
| Oxytocin characteristics  |                                 |                                   |         |
| Oxytocin induction, n (%) | 52 (31.7)                       | 71 (39)                           | 0.156   |
| Postanalgesia oxytocin administration, n (%) | 34 (20.7)      | 30 (16.5)                         | 0.309   |
| Cervix, cm               | 2.3 ± 1.5                       | 2.2 ± 1.0                         | 0.305   |
| Duration, hr             | 4.4 ± 1.8                       | 3.9 ± 1.5                         | 0.029   |
| Total consumption, IU    | 1.5 ± 0.9                       | 1.4 ± 0.7                         | 0.125   |
| Drug cost, USD ($)        | 5.70 ± 2.06                     | 5.87 ± 1.95                       | 0.603   |
| Ropivacaine              | —                               | 4.06 ± 1.47                       | 0.291   |
| Sufentanil               | —                               | —                                 | —       |
| Total                    | 5.70 ± 2.06                     | 9.76 ± 3.54                       | <0.0001 |

USD = US dollar.

Bold emphasized values indicate statistically significant when P was set at < 0.05.

* Patients who underwent Cesarean section after the analgesia initiation were excluded from the per protocol (PP) analysis. The data herein were calculated based on the intention-to-treat (ITT) sample size, that is, n = 250 with each group.

† These values were calculated from those patients received postanalgesia oxytocin but without oxytocin induction.

### TABLE 5. Fetal Characteristics

|                          | Sole Local Anesthesia (n = 164) | Local Anesthesia + Opiod (n = 182) | P Value |
|--------------------------|---------------------------------|-----------------------------------|---------|
| Apgar scoring (0–10)     |                                 |                                   |         |
| 1-minute                 | 10 (7–10)                       | 10 (6–10)                         | 0.006   |
| 5-minute                 | 10 (9–10)                       | 10 (9–10)                         | 0.233   |
| Incidence of 1-minute Apgar ≤7, n (%) | 2 (1.2)                  | 2 (1.2)                           | 0.038   |
| Weight, g                | 3383 ± 379                      | 3449 ± 363                        | 0.101   |
| Aural temperature, °C    | 36.5 ± 0.2                      | 36.5 ± 0.2                        | 0.945   |
| Antibiotic administration, n (%) | 2 (1.2)                  | 1 (0.5)                           | 0.502   |
| Umbilical cord artery blood gas analysis |                     |                                   |         |
| pH value                 | 7.3 ± 0.1                       | 7.3 ± 0.1                         | 0.154   |
| pCO2, mm Hg              | 47.8 ± 12.1                     | 50.2 ± 11.1                       | 0.142   |
| pO2, mm Hg               | 21.8 ± 9.4                      | 19.6 ± 9.1                        | 0.058   |
| HCO3⁻, mmol/L            | 21.5 ± 2.4                      | 21.7 ± 2.5                        | 0.231   |
| Lactate, mmol/L          | 4.7 ± 1.5                       | 4.6 ± 1.5                         | 0.268   |
| BE, mmol/L               | −5.6 ± 2.6                      | −5.8 ± 2.5                        | 0.985   |

BE = base excess.

Bold emphasized values indicate statistically significant when P was set at < 0.05.

* Apgar scorings depicted as median (min – max), and compared with Wilcoxon rank test.
FIGURE 2. Kaplan–Meier curves for the length of labor. Arrows indicate median values of time. (A) Time of the 1st stage. Median time of the 1st stage was 480 minutes in both of the groups, $P = 0.741$. (B) Time of the 2nd stage. The difference in both of the median time was −3 minutes, $P = 0.463$. (C) Time of the 3st stage. Median time of the 3st stage was 9 minutes in both of the groups, $P = 0.533$. 
The overall incidence of intrapartum side effects in the sole local analgesic group was fewer than the combination group even though no statistical difference was detected. This kind of subtle difference is crucial clinically because no patient is willing to say “yes” to any type of side effect. The only side effect with the sole local analgesic group was maternal pyrexia. It is suggested that intrapartum pyrexia was common with epidural labor analgesia per se, with the mechanism unclear, irrespective of the opioidergic analgesics supplemented or not. Otherwise, 3 women in the combination group complained of pruritus, and additional 4 had fetal heart deceleration, all of them resolved spontaneously eventually. In a systematic review, intrathecal opioid versus epidural or systemic opioid analgesics in laboring women, intrathecal regimen resulted in a significant increase in the risk of maternal pruritus and fetal heart deceleration.

In this study, the overall cesarean rate based on an ITT analysis was approximately 10% in both groups. No perineal laceration more than 2 degree was observed, indicating that no partial or complete obstetric anal sphincter injuries, which partially explained why no person was followed to have postpartum fecal or urine incontinence.

Otherwise, Wong and colleagues found that intrathecal opioid use significantly shortened the 1st stage of labor compared with the systemic opioid administration but in our trial, we did not find a prolonged duration of the 1st stage of labor in women received sole ropivacaine compared with the combination group. Meanwhile, similar labor duration was under the similar proportion of women receiving either oxytocin induction or augmentation of labor. Although a statistically longer duration of postanalgesia oxytocin augmentation in the sole local analgesic group was observed, the overall oxytocin consumption was not statistically different between the 2 groups. More important, no increased cesarean delivery and instrument vaginal delivery was observed due to the longer duration of oxytocin administration in the sole local analgesic group in our study, which was in line with previous reports. Although epidural analgesia per se or intrapartum oxytocin administration was suspected to interfere with normal breastfeeding, the breastfeeding rates in either group was over 99%.

Neonates in the combination group had significantly lower 1-min Apgar scoring than the sole local analgesic group. This suggested that sufentanil supplement exert significant impact on neonatal 1-min Apgar ratings. Controversial results exist with respect to the influence of opioid exposure on neonatal Apgar scoring. Wang et al found the common doses of fentanyl and sufentanil used with an epidural/spinal technique in labor analgesia were safe for neonates with a similar incidence of 1-min Apgar <7. In addition, Ciccarelli et al found the use of sufentanil in the combined spinal-epidural labor analgesia did not change Apgar scorings of the newborns. However, a systemic review found that neonates with parenteral opioid exposure had a higher incidence of poor 1-min Apgar scorings and need more naloxone. So, considering the effect of sufentanil exposure on neonatal Apgar scoring, it is necessary to consider the neonatal risk of sufentanil supplement for labor analgesia.

Some limitations of our study need to be acknowledged before drawing conclusion. First, we only observed the primiparous women with a single, term fetus, so the results in other populations need to be tested further. Second, this study was confined to a specific ropivacaine and sufentanil concentration combined with certain PCEA protocol without background infusion, whether the results may be applied to other analgesics such as bupivacaine, fentanyl, or other epidural labor analgesia regimens such as PCEA with a continuous infusion dose remains unclear. Further, other than lower neonatal Apgar scoring associated with sufentanil supplement, the long-term detriments of opioids exposure on neonates were not explored in this study and deserved further investigation.

In summary, this study provides robust evidence that the sole ropivacaine produced a comparable analgesic efficacy as the combination of both ropivacaine and sufentanil for labor. Considering the analgesia-related more side effects, higher cost, and lower neonatal Apgar scoring associated with sufentanil supplement, it is worth reconsidering the rationality of supplementing opioids with local anesthetics for epidural labor analgesia.

REFERENCES

1. Wong CA. Advances in labor analgesia. Int J Women Health. 2010;1:139–154.
2. Anim-Somuah M, Smyth RM, Jones L. Epidural versus non-epidural or no analgesia in labour. Cochrane Database Sys Rev. 2011;12:CD000331.
3. Ngan Kee WD, Khaw KS, Ng FF, et al. Synergistic interaction between fentanyl and bupivacaine given intrathecally for labor analgesia. Anesthesiology. 2014;120:1126–1136.
4. Halpern SH, Iosovich A. Epidural analgesia and breast-feeding. Anesthesiology. 2005;103:1111–1112.
5. Tian F, Wang K, Hu J, et al. Continuous spinal analgesia with sufentanil in labor analgesia can induce maternal febrile responses in puerperas. Int J Clin Exp Med. 2013;6:334–341.
6. Reynolds F. The effects of maternal labour analgesia on the fetus. Best Pract Res Clin Obstet Gynaecol. 2010;24:289–302.
7. Nakamura G, Ganem EM, Rugolo LM, et al. Effects on mother and fetus of epidural and combined spinal-epidural techniques for labor analgesia. Rev Assoc Med Bras. 2009;55:405–409.
8. Golub MS, Eisele JH Jr, Kuhnert BR. Disposition of intrapartum narcotic analgesics in monkeys. Anesth Anal. 1988;67:637–643.
9. Golub MS, Eisele JH Jr, Donald JM. Obstetric analgesia and infant outcome in monkeys. Neonatal measures after intrapartum exposure to meperidine or alfentanil. Am J Obstet Gynecol. 1988;158:1219–1225.
10. Golub MS, Eisele JH Jr, Donald JM. Obstetric analgesia and infant outcome in monkeys: infant development after intrapartum exposure to meperidine or alfentanil. Am J Obstet Gynecol. 1988;159:1280–1286.
11. Ferguson SA, Ward WL, Paule MG, et al. A pilot study of preemptive morphine analgesia in preterm neonates: effects on head circumference, social behavior, and response latencies in early childhood. Neurotoxicol Teratol. 2012;34:47–55.
12. Ahirwar A, Prakash R, Kushwaha BB, et al. Patient controlled epidural labour analgesia (PCEA): a comparison between ropivacaine, ropivacaine-fentanyl and ropivacaine-clonidine. J Clin Diagn Res. 2014;8:GC09–GC13.
13. Craig MG, Grant EN, Tao W, et al. A randomized control trial of bupivacaine and fentanyl versus fentanyl-only for epidural analgesia during the second stage of labor. Anesthesiology. 2015;122:172–177.
14. Wang F, Shen X, Guo X, et al. Epidural analgesia in the latent phase of labor and the risk of cesarean delivery: a five-year randomized controlled trial. Anesthesiology. 2009;111:871–880.
15. Li B, Wang H, Gao C. Bupivacaine in combination with fentanyl or sufentanil in epidural/intrathecal analgesia for labor: a meta-analysis. J Clin Pharmacol. 2015;55:584–591.
16. Wang X. Adhere to the principle “primum non nocere”: a documentary of the pioneer scientist in labor pain control in China. Sci Insights. 2014;6:112–114.

17. National Collaborating Centre for Women’s and Children’s Health. Intrapartum Care: Care of Healthy Women and Their Babies During Childbirth. London: National Collaborating Centre for Women’s and Children’s Health, 2007.

18. Lv BS, Wang W, Wang ZQ, et al. Efficacy and safety of local anesthetics bupivacaine, ropivacaine and levobupivacaine in combination with sufentanil in epidural anesthesia for labor and delivery: a meta-analysis. Curr Med Res Opin. 2014;30:2279–2289.

19. Lin R, Tao Y, Yu Y, et al. Intravenous remifentanil versus epidural ropivacaine with sufentanil for labour analgesia: a retrospective study. PLoS ONE. 2014;9:e112283.

20. Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med. 2001;38:639–643.

21. Bodian CA, Freedman G, Hossain S, et al. The visual analog scale for pain: clinical significance in postoperative patients. Anesthesiology. 2001;95:1356–1361.

22. Breivik H, Borchgrevink PC, Allen SM, et al. Assessment of pain. Br J Anaesth. 2008;101:17–24.

23. Grilo RM, Treves R, Preux PM, et al. Clinically relevant VAS pain score change in patients with acute rheumatic conditions. Joint Bone Spine. 2007;74:358–361.

24. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain. 2008;9:105–121.

25. Torvaldsen S, Roberts CL, Bell JC, et al. Discontinuation of epidural analgesia late in labour for reducing the adverse delivery outcomes with epidural analgesia. Cochrane Database Syst Rev. 2004;4:CD004457.

26. Pelley LS, Columb MO, Wagner DS, et al. Dose-dependent reduction of the minimum local analgesic concentration of bupivacaine by sufentanil for epidural analgesia in labor. Anesthesiology. 1998;89:626–632.

27. Ortner CM, Posch M, Roessler B, et al. On the ropivacaine-reducing effect of low-dose sufentanil in intrathecal labor analgesia. Acta Anaesthesiol Scand. 2010;54:1000–1006.

28. Katz JA, Bridenbaugh PO, Knarr DC, et al. Pharmacodynamics and pharmacokinetics of epidural ropivacaine in humans. Anesth Analg. 1990;70:16–21.

29. Lacassie HJ, Habib AS, Lacassie HP, et al. Motor blocking minimum local anesthetic concentrations of bupivacaine, levobupivacaine, and ropivacaine in labor. Reg Anesth Pain Med. 2007;32:323–329.

30. Sultan P, Murphy C, Halpern S, et al. The effect of low concentrations versus high concentrations of local anesthetics for labour analgesia on obstetric and anesthetic outcomes: a meta-analysis. Can J Anaesth. 2013;60:840–845.

31. Haydon ML, Larson D, Reed E, et al. Obstetric outcomes and maternal satisfaction in nulliparous women using patient-controlled epidural analgesia. Am J Obstet Gynecol. 2011;205:271 e1–271 e6.

32. Arendt KW, Segal BS. The association between epidural labor analgesia and maternal fever. Clin Perinatol. 2013;40:385–398.

33. Mardroosoff C, Domont L, Boulvain M, et al. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. BJOG. 2002;109:274–281.

34. Wong CA, Scavone BM, Peaceman AM, et al. The risk of cesarean delivery with neuraxial analgesia given early versus late in labor. N Engl J Med. 2005;352:655–665.

35. Steinberg J. Oxytocin augmentation during labor with epidural analgesia. Am Fam Physician. 2013;87:760–761.

36. Odent MR. Synthetic oxytocin and breastfeeding: reasons for testing an hypothesis. Med Hypotheses. 2013;81:889–891.

37. Dozier AM, Howard CR, Brownell EA, et al. Labor epidural anesthesia, obstetric factors and breastfeeding cessation. Matern Child Health J. 2013;17:689–698.

38. Wang K, Cao L, Deng Q, et al. The effects of epidural/spinal opioids in labour analgesia on neonatal outcomes: a meta-analysis of randomized controlled trials. Can J Anaesth. 2014;61:695–709.

39. Cicarelli DD, Silva RV, Frerichs E, et al. Combined spinal-epidural for labor analgesia: does the addition of sufentanil to the local anesthetic influence Apgar scores of the newborns? Rev Bras Anestesiol. 2007;57:272–279.

40. Leighton BL, Halpern SH. The effects of epidural analgesia on labor, maternal, and neonatal outcomes: a systematic review. Am J Obstet Gynecol. 2002;186 (suppl):S69–S77.