Original Article

The Dose-response of Intrathecal Ropivacaine Co-administered with Sufentanil for Cesarean Delivery under Combined Spinal-epidural Anesthesia in Patients with Scarred Uterus

Fei Xiao[1,2], Wen-Ping Xu[1], Yin-Fa Zhang[1], Lin Liu[1], Xia Liu[1,2], Li-Zhong Wang[1,2]

[1]Department of Anesthesia, Jiaxing Maternity and Child Care Hospital, Jiaxing, Zhejiang 314050, China
[2]Jiaxing Genetic and Reproductive Medicine Research Institute, Jiaxing, Zhejiang 314050, China

Abstract

Background: Spinal anesthesia is considered as a reasonable anesthetic option in lower abdominal and lower limb surgery. This study was to determine the dose-response of intrathecal ropivacaine in patients with scarred uterus undergoing cesarean delivery under combined spinal-epidural anesthesia.

Methods: Seventy-five patients with scarred uterus undergoing elective cesarean delivery under combined spinal-epidural anesthesia were enrolled in this randomized, double-blinded, dose-ranging study. Patients received 6, 8, 10, 12, or 14 mg intrathecal hyperbaric ropivacaine with 5 μg sufentanil. Successful spinal anesthesia was defined as a T_4 sensory level achieved with no need for epidural supplementation. The 50% effective dose (ED_{50}) and 95% effective dose (ED_{95}) were calculated with a logistic regression model.

Results: ED_{50} and ED_{95} of intrathecal hyperbaric ropivacaine for patients with scarred uterus undergoing cesarean delivery under combined spinal-epidural anesthesia (CSEA) were 8.28 mg (95% confidence interval [*CI*]: 2.28–9.83 mg) and 12.24 mg (95% *CI*: 10.53–21.88 mg), respectively.

Conclusion: When a CSEA technique is to use in patients with scarred uterus for an elective cesarean delivery, the ED_{50} and ED_{95} of intrathecal hyperbaric ropivacaine along with 5 μg sufentanil were 8.28 mg and 12.24 mg, respectively. In addition, this local anesthetic is unsuitable for emergent cesarean delivery, but it has advantages for ambulatory patients.

Key words: Cesarean Delivery; Dose-response; Ropivacaine; Scarred Uterus; Spinal

Introduction

Spinal anesthesia is widely used in patients undergoing cesarean delivery with rapid onset and reliable anesthesia.[1] Ropivacaine, a kind of new long-acting amide local anesthetic with structural and pharmacodynamic similarity to bupivacaine, has been advocated to use in patients for cesarean delivery under spinal anesthesia, because of the advantages of lower incidence of hypotension, short duration of motor block and less CNS, and cardiotoxic potential.[2-6]

Recently, with the second child policy in China being taken into effect, there were increasing numbers of patients with scarred uterus undergoing cesarean delivery in our hospital. Although dose-response studies of intrathecal ropivacaine in primiparas have been conducted, this clinical trials lead to different conclusions that the 95% effective dose (ED_{95}) of intrathecal ropivacaine for cesarean delivery ranges from 15.39 mg to 26.8 mg.[2,7] In addition, we suspect that the intrathecal optimal dose of ropivacaine for patients with scarred uterus may different with primiparas due to adhesion in lumbosacral area of epidural space that may result in difference of intrathecal local anesthetic spread. In this

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Address for correspondence: Dr. Li-Zhong Wang, Department of Anesthesia, Jiaxing Maternity and Child Care Hospital, Jiaxing, Zhejiang 314050, China
E-Mail: jxlzwang@sina.com

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study, we calculated logistic regression from a linear range of five different doses (6–14 mg) of intrathecal ropivacaine when co-administered with intrathecal 5 μg sufentanil, to determine the 50% effective dose (ED_{50}) and ED_{95} of intrathecal ropivacaine for patients with scarred uterus undergoing elective cesarean delivery.

Methods

Study subjects

This study was approved by the Ethics Committee in Jiaxing Maternity and Child Care Hospital, and written consent was received from all patients. Seventy-five patients with scarred uterus, who registered in Jiaxing Maternity and Child Care Hospital and admitted for cesarean delivery, were enrolled during a 3-month study period (from September 2014 to November 2014). Inclusion criteria were that patients with scarred uterus. Exclusion criteria were as follows: Any contraindication to combined spinal-epidural anesthesia (CSEA), body mass index greater than 35 kg/m^2, chronic hypertension, coagulation abnormality, platelet count less than 75×10^9/L, local or generalized sepsis, cord prolapsed, gestation less than 28 weeks, twin pregnancy, active labor, high-risk pregnancy, patient's age less than 25 years old or more than 40 years old, patient's height less than 150 cm or more than 170 cm, a nonreassuring fetal heart rate, or a suspected fetal pathology.

Before induction of spinal anesthesia

All patients received no premedication. On arrival in operation theater, each patient had an intravenous cannula inserted into a peripheral arm vein and received an infusion of 37°C Ringer's solution at the speed of 10 ($ml \cdot kg^{-1} \cdot h^{-1}$) before the start of CSEA. Standard monitoring included noninvasive blood pressure, pulse oximetry, and electrocardiogram. Based on a computer-generated grouping number sheets using EXCEL (version 2003; Microsoft company; USA), patients were randomly assigned to one of five groups (A, B, C, D, and E) to receive intrathecally 6, 8, 10, 12, and 14 mg ropivacaine respectively mixed with 5 μg sufentanil and 0.5 ml 10% glucose with normal saline added to make the total volume 3 ml in all cases. The mixed solution for spinal anesthesia was prepared under sterile conditions by an anesthesiologist who knew the patients grouping. CSEA was performed by an anesthesiologist who remained unknown to the patients grouping and the contents of the mixed solutions.

Induction of combined spinal-epidural anesthesia

The combined spinal-epidural anesthesia was conducted at L_{3-4} interspace with the patient lateral position using a needle-through-needle technique. In brief, a 16-gauge epidural Tuohy needle (Zhejiang Sujia Medical Medical Device Co., LTD., Jiaxing, Zhejiang) was inserted into the epidural space using the method of loss of resistance to air, and then a 26-gauge spinal needle (pencil point tip) was inserted into the intrathecal space passing through the Tuohy needle. After ascertaining the emergence of cerebrospinal fluid (CSF), the intrathecal mixed solution was injected into the intrathecal space within 15 s. Finally, the spinal needle was withdrawn and then an epidural catheter was threaded 2–3 cm cephaladly into the epidural space. The epidural catheter was gently aspirated and checked for the presence of blood or CSF. The patient was then positioned supine, with a right hip pad to minimize aortocaval compression.

Data collection

The success or failure of the spinal anesthesia was the primary endpoint. A success of spinal anesthesia was defined as a bilateral T_4 sensory block level to pinprick achieved within 15 min after the intrathecal drug administration, and no additional epidural analgesia was required during operation. A failure of spinal anesthesia was recorded when a T_4 sensory level was not obtained with 15 min after intrathecal drug administration, and/or additional epidural analgesia was required to complete surgery due to either a visual analog pain score (VAPS: 0–100; 0 means no pain and 100 means worst pain) ≥30 or the patient's request for additional analgesia despite a T_4 sensory level being achieved. Additional epidural anesthesia was epidural injection of 5 ml of 2% lidocaine, repeated every 5 min if necessary.

Sensory block level to pinprick was assessed at 2 min intervals for the first 15 min after intrathecal drug administration, then at 20 min intervals until the end of the surgery. The maximum sensory block and the time to maximum sensory block were recorded. Maximum Bromage scale and the duration of the motor block were also studied in each group. Motor block in the lower limbs was graded according to the modified Bromage scale (0: Able to flex extended leg at hip; 1: Able to flex knee but not flex extended leg; 2: Able to move foot only; 3: Unable to move foot). Duration of motor block was defined as the time from intrathecal injection to regression of motor block to a Bromage score of 0. Satisfaction of the operation condition (such as the degree of abdominal muscle relaxation) was assessed by the surgeon, ranked as good, moderate, or poor.

Noninvasive arterial blood pressure and heart rate were monitored at 1 min intervals during the time of intrathecal drug administration and baby delivery, and then at 5 min intervals until the end of the surgery. Hypotension was defined as systolic blood pressure less than 90 mmHg or a 25% decrease from the baseline level. Baseline blood pressure of the parturient was recorded in the preoperative room as the average of 3 readings taken 1 min apart. Phenylephrine 40 μg was given intravenously if necessary. Bradycardia was defined as heart rate less than 55 beats/min. Atropine was intravenously administrated when bradycardia occurred. The incidence of hypotension was recorded during the period from spinal injection to the baby delivery. The doses of phenylephrine or atropine administered were all recorded during this stage.

Neonate was evaluated using Apgar scores at 1 min and 5 min after delivery and umbilical artery blood gas analysis.

Patients' demographic data including age, body weight, height, gestational age, and duration of surgery were also recorded. Patients were interviewed in ward after surgery about nausea and pruritus using visual analog scale.

Statistical analysis

Using a Cochran-Armitage test for trend in proportions, a sample size of 15 patients per group as obtained based on five groups with ropivacaine dosage values of 6, 8, 10, 12, and 14 mg and proportions of success equal to 0.4, 0.5, 0.6, 0.7, and 0.8, respectively.

Statistical analysis was performed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Numerical variables were presented as mean and standard deviation (SD) or median (range) where appropriate. Categorical data (incidence data) were presented as numbers or percentages. Means with normally distributed were analyzed by one-way analysis of variance, medians and means with nonnormally distributed were analyzed by Mann-Whitney U-test, incidence data were analyzed by Fisher's exact test. The ED_{50} and ED_{95} of intrathecal ropivacaine were calculated by a logistic regression model described by Khaw *et al*.[2] and Chen *et al*.[7] previously. Logistic regression was used to identify possible significant factors influencing effective or ineffective anesthesia. Statistical significance was defined as $P < 0.05$ (two-sided).

Results

Eighty-two patients with scarred uterus were assessed for eligibility, among them 75 patients were enrolled and randomly assigned into one of the five groups. All of the 75 patients finished the study and were included in the final analysis. Five patients refused to participate; two patients did not meet the inclusion criteria. There were no any differences in age, weight, height, gestational age, duration of surgery, 1 min and 5 min neonate Apgar Scores, and fetal umbilical artery blood pH among groups (all $P > 0.05$) [Table 1].

The percentage of successful spinal anesthesia at different doses of ropivacaine is shown in Figure 1. Logistic regression plots were drawn for the success of spinal anesthesia as shown in Figure 2. The 0.5 and 0.95 y-intercepts were used to calculate the ED_{50} and ED_{95} of intrathecal ropivacaine for both plots. The ED_{50} and ED_{95} of intrathecal ropivacaine co-administered with 5 μg sufentanil were 8.28 mg (95% confidence interval [*CI*]: 2.28–9.83 mg) and 12.24 mg (95% *CI*: 10.53–21.88 mg), respectively.

Epidural supplementation was required in 12 cases in Group A, 7 cases in Group B, 3 cases in Group C, 1 case in Group D, and none in Group E. The maximum sensory block level was similar among groups ($P > 0.05$) [Table 2]. There was no difference in the onset time to maximum sensory level ($P > 0.05$) [Table 2]. The maximum Bromage score is higher in Group D ($\chi^2 = 19.55, 19.55, 19.55$, respectively, $P < 0.05$) and Group E ($\chi^2 = 16.81, 16.81, 16.81$, respectively, $P < 0.05$) than in other three groups [Table 2]. The duration of motor block in the case of successful anesthesia is longer in Group D ($U = 0, -15, 0$, respectively, $P < 0.05$) and Group E ($U = 0, 0, -63$, respectively, $P < 0.05$) than in other three groups [Table 2]. There were no significant differences among groups in the incidence of hypotension, nausea, vomiting, shivering, and pruritus [Table 2].

Satisfaction of the operation condition (such as the degree of abdominal muscle relaxation), assessed by the surgeon, was poorer in Group A ($\chi^2 = 9.64, 32.40$, and 13.30, respectively, $P < 0.05$) and Group B ($\chi^2 = 4.44, 10.80$, and 7.18, respectively, $P < 0.05$) than those in the other three groups [Table 3].

Discussion

It is well-accepted that there might be adhesion in lumbosacral area of epidural space in parturients with scarred uterus, which could change the volume of this area and will associate with changes in CSF volume of this area. The CSF volume in the lumbosacral area has proven to be one of the most important determinants of intrathecal local anesthetic spread which means that a smaller volume cause more extensive drug spread and result less requirement of local anesthetics for spinal anesthesia.[8,9] In addition, the fact that patients with scarred uterus may experience a longer

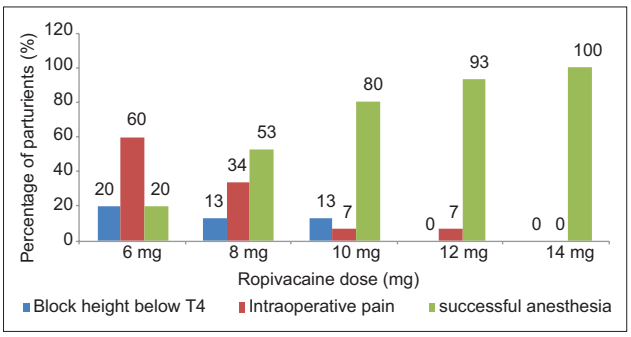

Figure 1: Anesthetic outcome for all patients.

Table 1: Demographic data, surgery data, and neonate Apgar scores of five groups (n=15 each group)

Items	Group A	Group B	Group C	Group D	Group E
Age (years)	32.3 (5.2)	29.5 (3.1)	29.3 (3.3)	31.1 (4.5)	32.5 (5.2)
Height (cm)	160.7 (5.6)	161.2 (5.6)	163.0 (6.1)	163.1 (4.6)	160.3 (4.8)
Weight (kg)	68.6 (6.3)	67.0 (4.3)	68.3 (3.6)	67.5 (3.2)	68.0 (4.4)
Gestational age (weeks)	38.8 (0.7)	38.5 (0.9)	38.4 (0.6)	38.7 (0.8)	38.4 (0.6)
Duration of surgery (min)	64.9 (6.5)	62.5 (9.3)	63.8 (6.2)	65.1 (9.4)	64.1 (10.3)
1 min Apgar scores	9.0 (0.8)	9.0 (0.9)	8.8 (0.8)	9.2 (0.9)	8.9 (1.1)
5 min Apgar scores	9.1 (0.6)	9.5 (0.6)	9.1 (0.3)	9.3 (0.5)	9.3 (0.6)
Umbilical artery pH	7.36 (0.06)	7.34 (0.04)	7.35 (0.05)	7.36 (0.08)	7.34 (0.05)

Values were presented as mean (SD). Compared between five groups, there were no significant differences, P>0.05. SD: Standard deviation.

Table 2: Anesthetic characteristics and side effects of five groups (n=15 each group)

Items	Group A	Group B	Group C	Group D	Group E
Sensory level (to pinprick) (at 15 min after intrathecal drug administration)	T_4 (T_{4-6})	T_4 (T_{3-7})	T_4 (T_{3-6})	T_4 (T_{3-4})	T_4 (T_{3-4})
Onset time to maximum sensory level (min), mean (SD)	10.5 (1.4)	10.5 (1.1)	9.7 (1.3)	9.3 (1.2)	8.4 (1.1)
Maximum Bromage scale 0–1–2–3 (at 15 min after intrathecal drug administration)	5–8–2–0	1–8–6–0	0–4–11–0	0–0–2–13*	0–0–3–12*
Duration of motor block (in the case of successful anesthesia) (min), median (range)	38 (35–45)	55 (38–73)	68 (50–95)	116 (100–160)*	125 (98–170)*
Hypotension (period from spinal injection to the baby delivery), n (%)	3 (20)	5 (33)	4 (27)	6 (40)	8 (53)
Requirement of phenylephrine (period from spinal injection to the baby delivery) (μg), median (range)	0 (0–40)	0 (0–80)	0 (0–80)	0 (0–80)	40 (0–80)†
Nausea and vomiting, n (%)	3 (20)	2 (13)	2 (13)	3 (20)	3 (20)
Shivering, n (%)	4 (27)	3 (20)	3 (20)	3 (20)	5 (33)
Pruritus, n (%)	7 (47)	8 (53)	6 (40)	8 (53)	6 (40)

*P<0.05, compared with Groups A, B, and C; †P<0.05, compared with other groups. SD: Standard deviation.

Table 3: Satisfaction to operation condition assessed by surgeon

Rank	Group A	Group B	Group C	Group D	Group E
Good	4	6	12*	14*	13*
Moderate	10	9	3*	1*	2*
Poor	1	0	0	0	0

Data were presented as patients' number. *P<0.05, compared with Groups A and B.

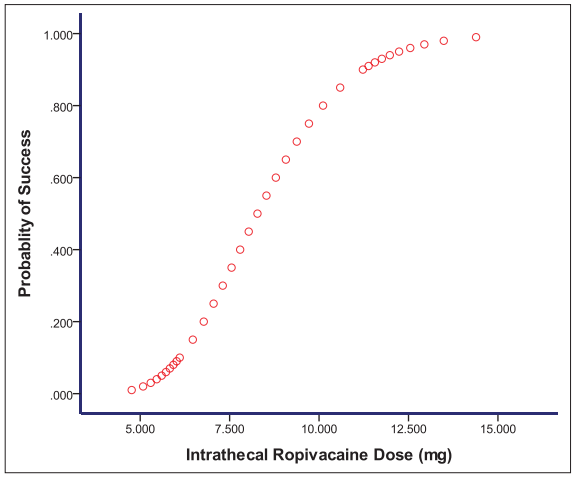

Figure 2: Logistic regression plot of the probability of successful spinal anesthesia versus intrathecal ropivacaine dose. The probability of 0.5 and 0.95 was used for deriving the 50% effective dose and 95% effective dose of intrathecal ropivacaine to achieve successful spinal anesthesia for cesarean delivery.

surgery than the parturients when undergoing cesarean delivery for the first time, which requires that the distant effect of spinal anesthesia should meet a higher reliability. Regarding the above two reasons, data from primiparas may not be applied to patients with scarred uterus directly. Therefore, in this study, we determined to explore the ED_{50} and ED_{95} of intrathecal ropivacaine for patients with scarred uterus undergoing elective cesarean delivery.

The present study found that the ED_{50} and ED_{95} of intrathecal ropivacaine for cesarean delivery in patients with scarred uterus were 8.28 mg (95% *CI*: 2.28–9.83 mg), and 12.24 mg (95% *CI*: 10.53–21.88 mg), respectively, when co-administered with intrathecal 5 μg sufentanil. To our knowledge, this is the first time to determine the ED_{50} and ED_{95} of intrathecal ropivacaine in patients with scarred uterus undergoing cesarean delivery. A previous studies conducted by Khaw *et al.*[2] suggested that the ED_{50} and ED_{95} of intrathecal plain ropivacaine for cesarean delivery were 16.7 mg (95% *CI*: 14.1–18.8 mg) and 26.8 mg (95% *CI*: 23.6–34.1 mg). Another dose-response study with hyperbaric ropivacaine for cesarean delivery in Chinese women conducted by Chen *et al.*[7] determined that the ED_{50} and ED_{95} were 10.37 mg (95% *CI*: 5.23–11.59 mg) and 14.29 mg (95% *CI*: 13.03–19.81 mg). These studies were inconsistent with our results. Except the factors mentioned above, the following factors may also contribute to the difference.

Firstly, intrathecal sufentanil, which was used in the present study, but was not used in the study of Khaw *et al.*[2] and Chen *et al.*,[7] may be an important factor. Sufentanil, a high lipophilic opioid with a higher affinity to opioid receptors, can reduce the dose requirements of intrathecal local anesthetics for cesarean delivery.[6,10-13] Although a wide range dose of sufentanil from 2.5 μg to 20 μg has been studied,[6,11,14-18] we choose 5 μg sufentanil as intrathecal adjuvant in the current study based on the following findings. Braga Ade *et al.*[14] compared three different doses (2.5, 5 and 7.5 μg) of intrathecal sufentanil co-administered with hyperbaric bupivacaine 12.5 mg for caesarean delivery and found that the addition of both sufentanil 5 and 7.5 μg could provide adequate anesthesia, but the addition of sufentanil of 7.5 μg was associated with a higher incidence of undesirable pruritus. In addition, Qian *et al.*[15] compared intrathecal hyperbaric ropivacaine 10 mg combined with sufentanil 5 μg with intrathecal hyperbaric ropivacaine 15 mg under CSEA for cesarean delivery and found that the combination of hyperbaric ropivacaine 10 mg with sufentanil 5 μg produced effective spinal anesthesia for caesarean delivery with significantly less hypotension, vomiting, and shivering, shorter duration of motor blockade, and longer lasting analgesia.

Secondly, dose-response studies estimating the potency of intrathecal local anesthetic for cesarean delivery used varied definitions of a successful block, thus resulting in some difficulties for the direct comparison of the results among trials. In the above two studies, they defined that an upper sensory level to pin prick of T_7 or above was achieved and no intraoperative epidural supplement was required as a successful block.[2,7] Criteria of successful spinal anesthesia of our study are stricter than that of the two previous studies, which could result in less cases of successful spinal anesthesia in our study, but may improve patient and surgeon's satisfaction of surgery. In our study, in the group of lower dose of intrathecal of ropivacaine, surgeons complained frequently about the condition of muscle relaxation. One can assume that the local concentration of ropivacaine was probably low at the distant effect sites in the lower ropivacaine dose groups, leading to inadequate potency for providing surgical anesthesia in these groups of patients. As previous studies reported,[19,20] the initial T_6 block to pinprick did not reliably predict overall success. However, in this study a successful block was defined as one that resulting in a sensory block to T_4 level within 15 min after intrathecal injection, and no additional epidural analgesia being required during operation, which may minimize the risk of inadequate anesthesia.

Thirdly, different baricity of intrathecal solution of ropivacaine may be another factor. The solution of ropivacaine used in our study was hyperbaric while the solution used in Khaw *et al*. study was plain. Previous studies have shown that intrathecal hyperbaric ropivacaine may produce more predictable and reliable anesthesia than isobaric or hypobaric ropivacaine and less duration of motor block.[21-24]

Eventually, the position of the patient and the surgical technique should also be taken into account. It has shown that not only the baricity of injectate but also the position of the patient primarily determines the spread of intrathecal local anesthetics.[25,26] In Khaw *et al.* study, spinal anesthesia was finished with the patient in sitting position, whereas the patient in the current study was in a lateral position. Especially in pregnant women, the width of the hips is usually larger than that of the shoulders which result in a head-down tilt when lying in the lateral position.[27] And this may contribute to less failure of spinal induction in our study. Additionally, the surgical technique involved exteriorization of the uterus, a profound surgical stimulus that may be expected to increase anesthetic requirement. In our study, in the lower dose of ropivacaine group, many patients experienced late anesthetic failure at this stage of surgery.

A recent study compared the effect of adding sufentanil to intrathecal ropivacaine reported that the ED_{50} of ropivacaine for cesarean delivery was similar to our results (8.1 vs. 8.28 mg).[6] Although Dixon's up-and-down method combined with probit analysis method is suitable for calculation of ED_{50} designed in the study by Chen *et al*.,[6] it was obviously that our dose-response study methodology was more accurate to calculate ED_{95}, which is more relevant for clinical practice than the ED_{50}. In this study, the incidence of hypotension in Group D (the dose closed to ED_{95}) was higher than that in Group B (the dose closed to ED_{50}), but there was no statistical difference between two groups. Previous studies showed that lowering the spinal dose of local anesthetics could reduce the incidence of maternal hypotension for patients undergoing cesarean delivery.[15,28-32] The different finding in the present study may be related to the small sample size, and further study about intrathecal dose relevant hypotension of ropivacaine is needed.

Interestingly, there was no difference in the maximum height of sensory block among groups. However, the success rate of effective anesthesia was significantly different. Our results revealed that this difference was related to dosage. This was also found in the study of Khaw *et al*., and they suggested that the quality or density of the block is also important.[2] Therefore, in our study, to improve the quality of spinal anesthesia, we added 5 μg sufentanil to intrathecal ropivacaine.

We found there was no difference in the onset time to highest sensory block among groups. As the time in the five groups was nearly 10 min, we did not suggest using intrathecal ropivacaine for emergent cesarean delivery which requiring a rapid onset. In the present study, we also found that a sufficient dose of ropivacaine is also needed when coadministrated with sufentanil for cesarean delivery. If the initial intrathecal dose of ropivacaine is less than ED_{95}, especially using the minimum local anesthetic dose (corresponding to ED_{50}), we suggested a CSEA technique should be applied in order to confirm the sufficient anesthesia during the surgery. We also found that the duration of motor block of spinal ropivacaine in the current study was shorter than equivalent potency bupivacaine or levobupivacaine in our clinic practice. And that was also reported from other's studies.[33,34] Consequently, we could suggest this local anesthetic has the advantages to be used for outpatient spinal anesthesia.

In summary, the present study demonstrated that the ED_{50} and ED_{95} of intrathecal ropivacaine for cesarean delivery in patients with scarred uterus were 8.28 mg and 12.24 mg when co-administered with intrathecal 5 μg sufentanil. And if a low dose of intrathecal ropivacaine were used, a CSEA technique should be utilized. Additionally, we do not recommend this local anesthetic for emergent cesarean delivery, but it has advantages to be used for ambulatory patients.

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Conflicts of interest

There are no conflicts of interest.

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