Clinical Trial/Experimental Study

Medicine®

OPEN

ED_{50} of intrathecal ropivacaine for cesarean section under prophylactic infusion of phenylephrine

A consort study

Wangping Zhang, MD[a,*], Hanbin Wu, MD[b]

Abstract

Background: Studies have reported that prophylactic continuous infusion of phenylephrine during spinal anesthesia for cesarean section can decrease the spread of local anesthetics. We investigated the ED_{50} of intrathecal hyperbaric ropivacaine in parturient women undergoing cesarean section under prophylactic infusion of phenylephrine.

Methods: Sixty parturient women were allocated into 2 groups in this prospective study. Group P received 0.5 mL kg^{-1} h^{-1} of phenylephrine (5 mg/50 mL) at the start of intrathecal injection, and Group C (control group) received the same volume of saline. The dose of intrathecal ropivacaine for each subject was decided through up-down allocation method. The initial dose was set as 7.5 mg. Successful anesthesia was defined as the level of T6 or above achieved within 15 minutes after intrathecal injection and no additional epidural drug or venous analgesia to complete operation. The Massey formula was applied to calculate the ED_{50} of intrathecal ropivacaine in both groups.

Results: The ED_{50} of hyperbaric ropivacaine determined by up-and-down method was 7.2 mg (95% confidence interval (CI), 6.8–7.6 mg) in the Group P, and 6.8 mg (95% CI, 6.4–7.2 mg) in the Group C, there was significant difference between the 2 groups ($P < .5$). The ED_{50} of intrathecal ropivacaine increases compared with Group C when phenylephrine is prophylactic infused to prevent spinal induced hypotension in cesarean section.

Conclusion: The ED_{50} of intrathecal hyperbaric ropivacaine is 7.2 mg when phenylephrine is prophylactic infused to prevent spinal induced hypotension in cesarean section, and more ropivacaine demands on spinal anesthesia for cesarean section (www.chictr.org.cn, registration number: ChiCTR-RIC-17011650).

Abbreviations: ASA = American Society of Anesthesiologists, BP = blood pressure, CSEA = combined spinal-epidural anesthesia, CSF = cerebrospinal fluid, ED_{50} = median effective dose, HR = heart rate, MAP = mean arterial blood pressure.

Keywords: cesarean section, phenylephrine, ropivacaine, spinal anesthesia

1. Introduction

Spinal anesthesia is a common technique for cesarean section.[1] However, the incidence of spinal induced hypotension is up to 80% in cesarean section, without any intervention measures, such as uterine displacement, intravenous fluid preload, and the use of vasopressors.[2] Recent studies have shown that prophylactic infusion of phenylephrine has more advantages in preventing spinal induced hypotension and fetal acidemia compared with a bolus administration.[3,4] However, evidences showed that prophylactic continuous infusion of phenylephrine can decrease the spread of intrathecal local anesthetic.[5,6] Therefore, we hypothesized that the dose of intrathecal local anesthetic would increase under prophylactic continuous infusion of phenylephrine to prevent spinal induced hypotension in cesarean section. To verify our hypothesis, we investigated the median effective dose (ED_{50}) of intrathecal hyperbaric ropivacaine in parturient women undergoing cesarean section under prophylactic infusion of phenylephrine using an up-down sequential allocation method.

2. Methods

Ethical approval was provided by the Hospital Ethical Committee (Chairman Prof X. Yin) on 4 May, 2017. Informed consent form was signed by all participants. From June to July 2017, 60 term parturient women undergoing elective cesarean section were enrolled in this study. Exclusion criteria were patients with body weight >90 kg, ASA >II, serious cardiovascular disease, pregnancy associated hypertension, and any contraindication to

Editor: Jianxun Ding.

This work was supported by Zhejiang Clinical Medical Research Foundation (2015-ZYC-A71).

Financial support and sponsorship: None declared.

Conflicts of Interest: None declared.

[a] Department of Anesthesiology, [b] Department of Obstetrics, Affiliated Women and Children's Hospital of Jiaxing University, Jiaxing, China.

[*] Correspondence: Wangping Zhang, Department of Anesthesiology, Affiliated Women and Children's Hospital of Jiaxing University, No. 2468, Zhonghuan East Road, Jiaxing, China (e-mail: zhang650679@163.com).

Medicine (2017) 96:44(e8319)

Received: 15 July 2017 / Received in final form: 17 September 2017 / Accepted: 25 September 2017

http://dx.doi.org/10.1097/MD.0000000000008319

spinal anesthesia. Parturient women were randomly allocated into one of Group C (infusion of saline) and Group P (prophylactic infusion of phenylephrine), based on a computer-generated random number list.

All the parturient women had no premedication. After entering the operating room, monitoring, including electrocardiogram, pulse oximetry, noninvasive blood pressure (BP), and heart rate (HR) was applied with anesthesia monitor (GE Company, Taipei, Taiwan) and venous access was established. An average of 3 consecutive measurements of BP and HR was defined as basal BP and basal HR. The mixed solution (hyperbaric ropivacaine + 25 μg fentanyl, total volume 2.5 mL in all cases) for spinal anesthesia was prepared by another anesthesiologist. Combined spinal-epidural anesthesia (CSEA) was performed by an anesthesiologist who was unknown to the dose of the mixed solutions. Lactate Ringer's solution was infused at rate of 10 mL $kg^{-1} h^{-1}$ after the intrathecal injection.

An 18-G Tuohy needle was introduced into the epidural space at the third and fourth lumbar vertebral interspace (L3, 4) via a midline approach in the left lateral position and a 27-G spinal needle was inserted the subarachnoid space via the Tuohy needle. After free flow of cerebrospinal fluid (CSF), the premixed solution (ropivacaine + fentanyl 25 μg) was injected over 10 seconds with the needle orifice directed cephalad. The patient was then turned to supine with a 10° tilt to the left side.

The dose of intrathecal ropivacaine administered was varied according to the up-and-down allocation method. In each group, the dose of intrathecal ropivacaine was 7.5 mg for the first patient. The initial dose of intrathecal ropivacaine at the next patient was determined by anesthetic effect of the previous patient under spinal anesthesia in each group. If spinal anesthesia of the previous patient was successful, the dose of intrathecal ropivacaine for the next patient was decreased by 0.5 mg gradient. If spinal anesthesia of the previous patient was failure, the dose of intrathecal ropivacaine for the next patient was increased by 0.5 mg. Surgery was permitted after T6 sensory block to pain was achieved. After delivery of the baby, 5 U oxytocin was infused intravenously.

A successful spinal anesthesia was defined as T6 sensory block level was achieved by pinprick within 15 minutes of the intrathecal injection according to previous studies[7–9] without additional epidural drug. In this study, the successful spinal anesthesia was defined as a bilateral T6 sensory block level of the spinal anesthesia was achieved by pinprick within 15 minutes after induce of spinal anesthesia and no additional epidural drug or venous analgesia to complete operation. Lidocaine was administrated to epidural space to rescue the induction of anesthesia if a bilateral T6 sensory block level was not achieved.

At the start of intrathecal injection, phenylephrine was infused at the rate of 0.5 mL $h^{-1} kg^{-1}$ (5 mg/50 mL) in Group P and saline was infused at the rate of 0.5 mL $h^{-1} kg^{-1}$ (50 mL) in Group C. If the systolic BP (SBP) was below 80% of the baseline or 80 mmHg, a bolus of 50 μg phenylephrine was administered. The infusion was stopped when the SBP was >20% of baseline or 140 mmHg. Bradycardia was defined as heart rate <60 beats per minutes, and treated with a bolus of 0.3 mg atropine intravenously.

2.1. Measurements

The primary outcome was the effect of spinal anesthesia. The secondary outcomes were the characteristics of spinal anesthesia and the side effects of spinal anesthesia. BP and HR were recorded from the beginning of intrathecal injection at 1-minute intervals before the newborn delivery, and then at 3-minute intervals until the end of the surgery. Sensory block level was assessed using a pink needle. The maximum of sensory block level was recorded. The onset time of sensory block was defined as the time from intrathecal injection to a T10 sensory block level achieved. The duration of spinal anesthesia was defined as the period from intrathecal injection to the first occasion when the patient complained of incisional pain. Motor block was assessed using a modified Bromage score[10] [0 = no motor loss, 1 = inability to flex hip, 2 = inability to flex hip and knee, 3 = inability to flex hip, knee, and ankle]. At the end of the surgery, patients were asked to the level of satisfaction during surgery (1 = excellent; 2 = good; 3 = bad). Side effects of spinal anesthesia (hypotension, bradycardia, pruritus, shivering, nausea, and vomiting) were recorded. Umbilical arterial blood gas was analyzed immediately after delivery. The neonatal Apgar score at the 1st and 5th minutes was assessed.

2.2. Statistical analysis

According to the previous study[9,11] and our pilot study, a sample size of 30 patients for each group was determined in this study, because sample size is regarded as adequate when 6 pairs of reversal of sequence are achieved. Demographic data were collected and are presented as count or mean ± SD as appropriate. Nominal data were analyzed using the Chi-square test, normally distributed continuous data were analyzed using Student's *t* test and non-normally distributed continuous data were analyzed using nonparametric Mann–Whitney *U* test. Normal distribution was determined using the Kolmogorov–Smirnov test. Statistical analysis was performed with SPASS 19.0 soft (SPASS Inc., Chicago, IL). Statistical significance was defined as $P < .05$.

3. Results

The consort diagram of study is showed in Fig. 1. Sixty-two patients were assessed for eligibility (2 were excluded), then 60 patients were enrolled and randomly assigned into the Group P (n = 30) or the Group C (n = 30). All the patients finished the study. There were no significant differences in the data of parturient women between the control group and the group P (Table 1).

The ED_{50} of hyperbaric ropivacaine determined by up-and-down method was 7.2 mg (95% confidence interval (CI), 6.8–7.6 mg) in the Group P, and 6.8 mg (95% CI, 6.4–7.2 mg) in the Group C. There was significant difference in the ED_{50} of ropivacaine between the 2 groups ($P < .05$). "◆"represents a successful spinal anesthesia and "■" represents a failure spinal anesthesia (Fig. 2).

Characteristics of spinal anesthesia are presented in Table 2. The maximum sensory block level was similar between the groups ($P > .05$). The onset time to T_{10} were similar between groups (5.7 ± 1.2 vs 5.6 ± 1.3, $P > .05$). The duration of spinal anesthesia was also similar between the groups (57 ± 16 vs 54 ± 13, $P > .05$). The modified Bromage score was similar between the groups ($P > .05$).

Intraoperative mean arterial blood pressure (MAP) was higher at time point 1, 2, and 3 in Group P than in Group C (Fig. 3). The incidence of side effects of spinal anesthesia, such as hypotension, nausea and vomiting, shivering was shown in Table 3. The incidence of hypotension was significantly higher in Group C than in Group P (6.7% vs 43.3%, $P < .05$). The umbilical arterial

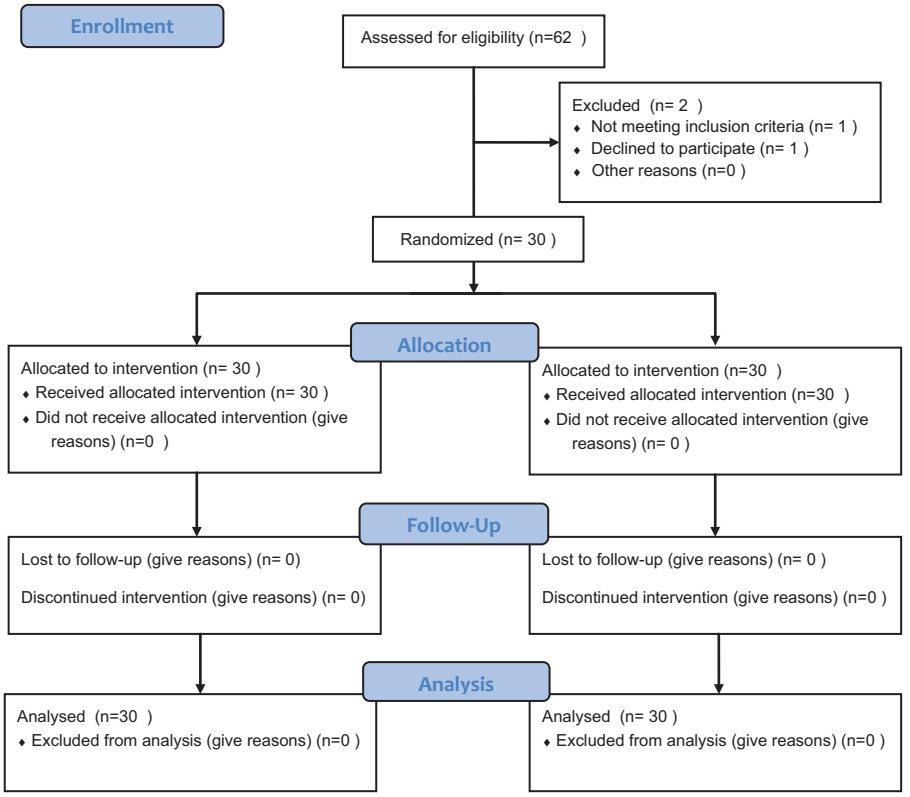

Figure 1. Flow diagram of study.

pH immediately after delivery was higher in Group P than in Group C (7.25 ± 0.06 vs 7.22 ± 0.05, $P < .05$).

4. Discussion

We found that the ED_{50} of intrathecal hyperbaric ropivacaine combined with 25 μg fentanyl for cesarean section with or without prophylactic continuous infusion of phenylephrine to prevent post-spinal hypotension were 7.2 mg (95% CI, 6.8–7.6 mg) and 6.8 mg (95% CI, 6.4–7.2 mg), respectively. Our study indicated also that the ED_{50} of intrathecal hyperbaric ropivacaine increased when phenylephrine was prophylactic infused to prevent spinal induced hypotension in cesarean section.

It is well known that pregnancy causes the dilation of epidural venous, which results in a reduction of CSF volume in lumbar area.[5] Subsequently, it brings about the decrease of requirements of intrathecal local anesthetics or fastening the spread of intrathecal local anesthetics. However, prophylactic infusion of phenylephrine to prevent spinal induced hypotension can shrink the epidural veins and offset the effect of epidural venous dilation in parturient women, which maybe weaken the pregnancy-induced decrease in intrathecal anesthetic requirement. It was the

Table 1

Data of parturient women.

Index	Group P (n = 30)	Group C (n = 30)	*P*
Age, y	27.4 ± 4.1	26 .6 ± 3.2	.41
Height, cm	164.4 ± 4.3	162.5 ± 2.4	.42
Weight, kg	75 .2 ± 6.3	73.1 ± 7.2	.84
Gestational age, wk	39 .5 ± 1.3	39.7 ± 1.2	.60
Duration of surgery, min	38.5 ± 5.6	40.5 ± 6.4	.41
Apgar scores at 1st min	8.6 ± 1.3	8.9 ± 1.5	.41
Apgar scores at 5th min	8.7 ± 1.5	9.1 ± 1.8	.36
Umbilical artery pH	7.25 ± 0.06*	7.22 ± 0.05	.04

Data are presented as mean ± SD.
* $P < .05$.

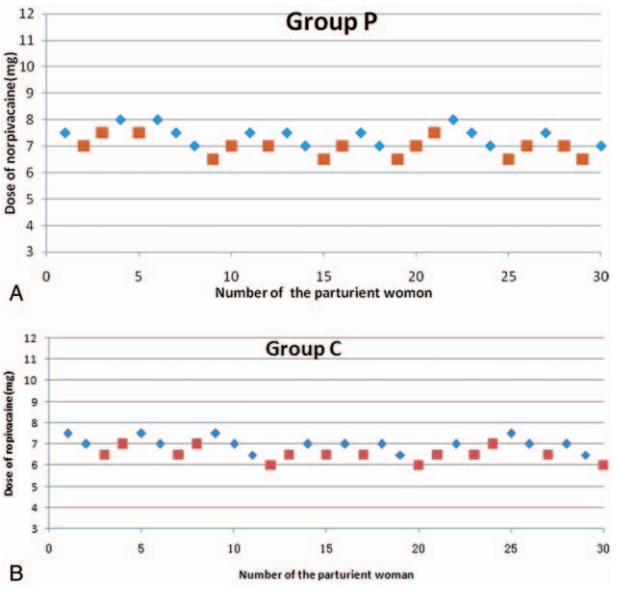

Figure 2. "◆"represents a successful spinal anesthesia and "■" represents a failure spinal anesthesia.

Table 2

Characteristic of spinal anesthesia with effective anesthesia.

Index	Group P (n=15)	Group C (n=16)	*P*
Maximum sensory block level [T4/T6] (n)	6/9	7/9	.76
Onset time of anesthesia, min	5.7±1.2	5.6±1.3	.26
Duration of anesthesia, min	57±16	54±13	.47

Data are presented as mean±SD, number (%) or median (range).

first possible reason that intrathecal anesthetic requirement increased above in the present study. A second possible reason was that phenylephrine caused increased vascular tension, which limited the spread of local anesthetic.[5] Changes of intracranial pressure would subsequently result in the redistribution of CSF between the cranial cavity and vertebral canal. Therefore, the factors brought about change of intracranial pressure, such as infusing phenylephrine, would also lead to the redistribution of CSF and influence the spread of anesthetics. On the condition of prophylactic infusion of phenylephrine, it brought about a higher intracranial pressure and a shift of CSF from the cranial cavity to the vertebral canal, and limited the spread of local anesthetics. Previous studies was reported that intravenous infusion of phenylephrine could decrease the spread of intrathecal isobaric levobupivacaine and hyperbaric bupivacaine for cesarean section.[6,12] However, the clinical significance of above findings still was unknown. In this study, using up-and-down allocated method, we proved our hypothesis that the dose of intrathecal local anesthetic increased under prophylactic infusion of phenylephrine.

Sequential method is a classical method to measure the ED_{50} of drugs. Its advantage is to save sample size in clinics.[13] The ED_{50} of intrathecal bupivacaine has been investigated in the parturient women in previous studies, but the studies of the ED_{50} of intrathecal ropivacaine were few in the parturient women, especially under prophylactic infusion of phenylephrine. So we investigated the ED_{50} of intrathecal ropivacaine on the condition of prophylactic infusion of phenylephrine. These results were similar with some of our study on ED_{50} of hyperbaric ropivacaine without prophylactic infusion of phenylephrine. However, Chen et al[14] and Zhen et al[15] reported that the ED_{50} of intrathecal hyperbaric ropivacaine coadministered with sufentanil 5 μg was 8.1 mg and 8.4 in cesarean section, respectively. The ED_{50} of intrathecal hyperbaric ropivacaine coadministered with opioids in their study was in disagreement with our study. As with the

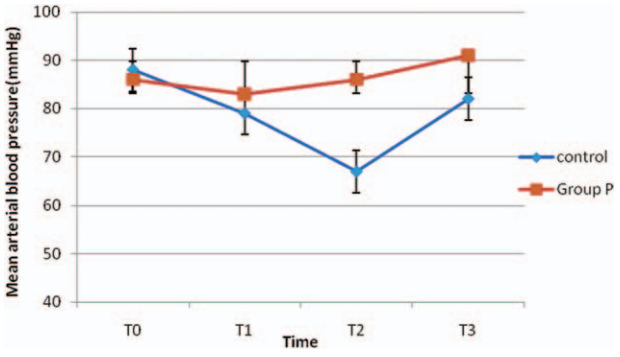

Figure 3. Intraoperative mean arterial pressure (MAP). MAP at time point 2, 3, and 4 was higher in Group P than in Group C (T0=Baseline MAP, T1=5 minutes after SA, T2=1 minute after delivery, T3=at end of surgery, SA=spinal anesthesia).

Table 3

Side effects of anesthesia.

Index	Group P (n=30)	Group C (n=30)	*P*
Hypotension	2 (6.7)*	13 (43.3)	.03
Bradycardia	4 (13.3)	1 (3.3)	.28
Nausea and vomiting	4 (13.3)	7 (23.3)	.59
Shivering	3 (10.0)	4 (13.3)	1.00
Pruritus	1 (3.3)	1 (3.3)	1.00

Data are presented as number (percent).
* $P<.05$.

ED_{50} of intrathecal hyperbaric bubivacaine, Tyagi et al[9] reported that the ED_{50} of intrathecal hyperbaric bubivacaine was 4.7 mg when coadministered with opioids in cesarean section. Firstly, Chen et al calculated the ED_{50} of intrathecal hyperbaric ropivacaine coadministered with sufentanil 5 μg, but the ED_{50} of intrathecal hyperbaric ropivacaine was 6.8 mg when combined with fentanyl 25 μg in our study, Zhen et al used regression analysis to calculate the ED_{50} of intrathecal hyperbaric ropipivacaine coadministered with sufentanil 5 μg, while we used the up-and-down method to measure the ED_{50} combined with fentanyl 25 μg. Additionally, successful spinal anesthesia was defined as a bilateral T6 sensory block level was achieved by pinprick within 15 minutes after induce of spinal anesthesia in our study, but within 10 minutes in their studies. Secondly, the position of patients had an effect on the results. CSEA was performed in a sitting position in their study, but patients were in left lateral position in our study. In parturient women, the intrathecal anesthesics spread more easily in left lateral position than in a sitting position.[16] Finally, other factors such as: individual difference, operation fashion and the duration of surgery could also have an effect on the results.

In the present study, prophylactic continuous infusion of phenylephrine could maintain the stability of the hemodynamic and decrease the incidence of spinal induced hypotension in cesarean section. Besides, the umbilical artery pH of newborns (7.25 vs 7.22) increased obviously. Our study also proved that prophylactic infusion of phenylephrine had more advantages on prevention spinal induced hypotension than bolus administration.

4.1. Limitations

Many factors influence the outcomes of the study. Height, vertebral length, transverse incision or vertical incision, duration of surgery and operative fashion, and so on. Besides, the ED_{50} of intrathecal hyperbaric ropivacaine was calculated by formula. Further studies are needed to do with large samples.

In conclusion, the ED_{50} of intrathecal hyperbaric ropivacaine is 7.2 mg when phenylephrine is prophylactic infused to prevent spinal induced hypotension in cesarean section, and more ropivacaine demands on spinal anesthesia for cesarean section.

Acknowledgments

The authors would thank all colleagues in the department of anesthesiology in this study.

References

[1] Tawfik MM, Hayes SM, Jacoub FY, et al. Comparison between colloid preload and crystalloid co-load in cesarean section under spinalanesthesia: a randomized controlled trial. Int J Obstet Anesth 2014;23:317–23.

[2] Moslemi F, Rasooli S. Comparison of prophylactic infusion of phenylephrine with ephedrine for prevention of hypotension in elective cesarean section under under spinal anesthesi: a randomized clinical trial. Iran J Med Sci 2015;40:19–26.
[3] Ngan Kee WD, Khaw KS, Ng FF, et al. Prophylactic phenylephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. Anesth analg 2004;98:815–21.
[4] Aragão FF, Aragão PW, Martins CA, et al. Comparison of metaraminol, phenylephrine and ephedrine in prophylaxis and treatment of hypotension in cesarean section under spinal anesthesia. Rev Bras Anestesiol 2014;64:299–306.
[5] Cooper DW, Jeyaraj L, Hynd R, et al. Evidence that intravenous vasopressors can affect rostral spread of spinal anesthesia in pregnancy. Anesthesiology 2004;101:28–33.
[6] Ngan Kee WD, Lee A, Khaw KS, et al. A randomized double-blinded comparison of phenylephrine and ephedrine infusion combinations to maintain blood pressure during spinal anesthesia for cesarean delivery: the effects on fetal acid-base status and hemodynamic control. Anesth Analg 2008;107:1295–302.
[7] Carvalho B, Durbin M, Drover DR, et al. The ED50 and ED95 of intrathecal isobaric bupivacaine with opioids for cesarean delivery. Anesthesiology 2005;103:606–12.
[8] Ginosar Y, Mirikatani E, Drover DR, et al. ED50 and ED95 of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. Anesthesiology 2004;100:676–82.
[9] Tyagi A, Kakkar A, Kumar S, et al. ED50 of hyperbaric bupivacaine with fentanyl for cesarean delivery under combined spinal epidural in normotensive and preeclamptic patients. Reg Anesth Pain Med 2012;37:40–4.
[10] Xu H, Li H, Zuo Y, et al. A multicenter study of the analgesic effects of epidural chloroprocaine after lower limb orthopedic surgery. J Clin Anesth 2016;35:313–20.
[11] Xiao F, Xu W, Feng Y, et al. Intrathecal magnesium sulfate does not reduce the ED50 of intrathecal hyperbaric bupivacaine for cesarean delivery in healthy parturients: a prospective, double blinded, randomized dose-response trial using the sequential allocation method. BMC Anesthesiol 2017;17:8.
[12] Cooper DW, Gibb SC, Meek T, et al. Effect of intravenous vasopressor on spread of spinal anaesthesia and fetal acid-base equilibrium. Br J Anaesth 2007;98:649–56.
[13] Dixon WJ. Staircase bioassay: the up-and-down method. Neurosci Biobehav Rev 1991;15:47–50.
[14] Chen X, Qian X, Fu F, et al. Intrathecal sufentanil decreases the median effective dose (ED50) of intrathecal hyperbaric ropivacaine for caesarean delivery. Acta Anaesthesiol Scand 2010;54:284–90.
[15] Zheng D, Wu G, Qin P, et al. Hyperbaric spinal anesthesia with ropivacaine coadministered with sufentanil for cesarean delivery: a dose-response study. Int J Clin Exp Med 2015;8:5739–45.
[16] Khaw KS, Ngan Kee WD, Wong M, et al. Spinal ropivacaine for cesarean delivery: a comparison of hyperbaric and plain solutions. Anesth Analg 2002;94:680–5.