Original Article

ED_{50} and ED_{95} of Intrathecal Bupivacaine Coadministered with Sufentanil for Cesarean Delivery Under Combined Spinal-epidural in Severely Preeclamptic Patients

Fei Xiao[1,2], Wen-Ping Xu[2], Xiao-Min Zhang[2], Yin-Fa Zhang[2], Li-Zhong Wang[2], Xin-Zhong Chen[1]

[1]Department of Anesthesia, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310006, China
[2]Department of Anesthesia, Jiaxing Maternity and Child Care Hospital, Jiaxing, Zhejiang 314005, China

Abstract

Background: Spinal anesthesia was considered as a reasonable anesthetic option in severe preeclampsia when cesarean delivery is indicated, and there is no indwelling epidural catheter or contraindication to spinal anesthesia. However, the ideal dose of intrathecal bupivacaine has not been quantified for cesarean delivery for severe preeclamptic patients. This study aimed to determine the ED_{50} and ED_{95} of intrathecal bupivacaine for severely preeclamptic patients undergoing elective cesarean delivery.

Methods: Two hundred severely preeclamptic patients are undergoing elective cesarean delivery under combined spinal-epidural anesthesia enrolled in this randomized, double-blinded, dose-ranging study. Patients received 4 mg, 6 mg, 8 mg, or 10 mg intrathecal hyperbaric bupivacaine with 2.5 μg sufentanil. Successful spinal anesthesia was defined as a T6 sensory level achieved within 10 minutes after intrathecal drug administration and/or no epidural supplement was required during the cesarean section. The ED_{50} and ED_{95} were calculated with a logistic regression model.

Results: ED_{50} and ED_{95} of intrathecal bupivacaine for successful spinal anesthesia were 5.67 mg (95% confidence interval [*CI*]: 5.20–6.10 mg) and 8.82 mg (95% *CI*: 8.14–9.87 mg) respectively. The incidence of hypotension in Group 8 mg and Group 10 mg was higher than that in Group 4 mg and Group 6 mg ($P < 0.05$). The sensory block was significantly different among groups 10 minutes after intrathecal injection ($P < 0.05$). The use of lidocaine in Group 4 mg was higher than that in other groups ($P < 0.05$). The use of phenylephrine in Group 8 mg and Group 10 mg was higher than that in the other two groups ($P < 0.05$). The lowest systolic blood pressure before the infant delivery of Group 8 mg and Group 10 mg was lower than the other two groups ($P < 0.05$). The satisfaction of muscle relaxation in Group 4 mg was lower than other groups ($P < 0.05$). There was no significant difference in patients' satisfaction and the newborns' Apgar score and the blood gas analysis of umbilical artery serum ($P > 0.05$).

Conclusion: Our study showed that the ED_{50} and ED_{95} of intrathecal bupivacaine for severely preeclamptic patients undergoing elective cesarean delivery were 5.67 mg and 8.82 mg, respectively. In addition, decreasing the dose of intrathecal bupivacaine could reduce the incidence of maternal hypotension.

Key words: Bupivacaine; Cesarean Section; Dose-response; Severe Preeclampsia; Spinal

Introduction

The most important pathophysiological change in patients with severe preeclampsia is systemic vasospasm, which can compromise the utero-placental perfusion.[1,2] Spinal anesthesia was considered as a reasonable anesthetic option in severe preeclampsia when cesarean delivery is indicated, and there is no indwelling epidural catheter or contraindication to spinal anesthesia.[3] However, spinal anesthesia-induced hypotension could worsen the utero-placental perfusion. So how to minimize the incidence of spinal-induced hypotension to ensure sufficient perfusion of utero-placental during cesarean section becomes one of the focuses to obstetricians and anesthesiologists. Limiting the dose of spinal, local anesthetics for caesarean delivery has been advocated for decreasing the incidence of spinal-induced hypotension in both normal intensive parturients and preeclamptic parturients.[4-7] Moreover, a reduction in spinal, local anesthetics may be achieved by a small dose of spinal opioid. Sufentanil, which is a more lipophilic opioid with a higher affinity to opioid receptors, a much higher analgesic potency than fentanyl or morphine,[8-10] has been shown to produce synergistic effects with local anesthetics, consequently to reduce spinal local anesthetics doses.[6,11] However, to the best of our knowledge, few previous studies

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Address for correspondence: Dr. Xin-Zhong Chen, Department of Anesthesia, Women's Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang 310006, China
E-Mail: chenxinz@zju.edu.cn

have determined the ideal dose of intrathecal bupivacaine when coadministered with sufentanil for cesarean delivery in severely preeclamptic parturients so far. In this study, we used logistic regression to determine the ED_{50} and ED_{95} of intrathecal bupivacaine for severely preeclamptic patients undergoing elective cesarean delivery, based on data from a linear range of four different doses (4–10 mg) of intrathecal bupivacaine when coadministered with intrathecal 2.5 μg sufentanil.

Methods

This study was approved by the Ethics Committee in our hospital, and written consent was received from all patients. Two hundred severely preeclamptic patients, who registered in our hospital and required to have a cesarean delivery, were enrolled during a 2 years (from 2012 to 2014) study period. Severe preeclampsia was defined by the presence of one of the following:[12,13] systolic arterial blood pressure (SBP) ≥160 mmHg, diastolic arterial blood pressure (DBP) ≥110 mmHg, symptoms of imminent eclampsia, proteinuria ≥300 mg/dL. Patients with hemolysis elevated liver enzymes, and low platelets syndrome were eligible for inclusion if the platelet count exceeded 75×10^9/L. Exclusion criteria were as follows:[14] any contraindication to combined spinal-epidural anesthesia (CSEA), body mass index >35 kg/m^2, chronic hypertension, coagulation abnormality, platelet count <75×10^9/L, local or generalized sepsis, cord prolapsed, gestation <28 weeks, twin pregnancy, active labor, or a non-reassuring fetal heart rate. Antepartum management of patients was based on the established protocol of our hospital: labetalol was administered to control blood pressure when SBP was 160 mmHg or higher, or DBP was 105 mmHg or higher, and magnesium sulfate therapy was initiated for prophylaxis of seizures.

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 mg·kg^{-1}·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 (Microsoft Office software), patients were randomly assigned to one of four groups (Group 4 mg, Group 6 mg, Group 8 mg and Group 10 mg) to receive intrathecally 4 mg, 6 mg, 8 mg, 10 mg bupivacaine respectively mixed with 2.5 μg sufentanil with normal saline added to make the total volume 2.5 ml in all cases. The mixed solution for spinal anesthesia was prepared under sterile conditions by an anesthesiologist who had known the patients grouping. CSEA was performed by an anesthesiologist who remained unknown to the patients grouping and the contents of the mixed solutions.

The CSEA was conducted at L3-4 interspace with the patient lateral position using a needle-through-needle technique. In brief, a 16-gauge epidural Tuohy needle was inserted to 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, the intrathecal mixed solution (diluted by cerebrospinal fluid to 3 ml) was injected into the intrathecal space within 15 seconds. 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 cerebrospinal fluid. The patient was then positioned supine, with a right hip pad to minimize aortocaval compression.

The success or failure of the spinal anesthesia was the primary data endpoint. A success of spinal anesthesia was defined, according to Carvalho *et al*. report,[15] as a bilateral T6 sensory block level to pinprick was achieved within 10 minutes of the intrathecal drug administration, and/or no additional epidural analgesia was required during operation. A failure of spinal anesthesia was recorded when a T6 sensory level was not obtained with 10 minutes after intrathecal drug administration, and/or additional epidural analgesia was required to complete surgery due to either a visual analogue pain score (VAPS: 0–100; 0 = no pain and 100 = worst pain) ≥30 or the patient's request for additional analgesia despite a T6 sensory level being achieved. Additional epidural analgesia was an epidural injection of 5 ml of 2% lidocaine, repeated every 5 minutes if necessary.

Sensory block level to pinprick was assessed at 30 seconds intervals for the first 10 minutes after intrathecal drug administration, then at 10 minutes intervals until the end of the surgery. Satisfaction of the operation condition (such as the degree of abdominal muscle relaxation) was assessed by the surgeon who performed the cesarean section, ranked as good, moderate, or poor. Subjective pain was assessed with VAPS at the following time points: skin incision, baby delivery, uterine exteriorization, peritoneal closure and skin closure. Patient's satisfaction was also rated as good, moderate or poor.

Noninvasive arterial blood pressure and heart rate were monitored at 1 minute intervals during the time of intrathecal drug administration and baby delivery, and then at 5 minutes intervals until the end of the surgery. Hypotension was defined as SBP < 110 mmHg or a 25% decrease from the baseline level. Phenylephrine, 40 μg, was given intravenously if necessary. Bradycardia was defined as heart rate <55 beats/min. Atropine was intravenously administrated when bradycardia occurred. The doses of phenylephrine or atropine administered were all recorded.

Neonate was evaluated using Apgar scores at 1 minute, 5 minutes 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 and postdural headache.

Statistical analysis was performed with SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). Numerical variables were presented as mean ± 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 (ANOVA), medians and nonnormally distributed means were analyzed by Mann–Whitney *U*-test, incidence data were analyzed by Chi-square test. The ED_{50} and ED_{95} of intrathecal bupivacaine were calculated by a logistic regression model described by Khaw *et al*.[16] and ourselves[17] 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

All the 200 patients finished the study. The demographic data were presented in Table 1. There were no significant differences in age, weight, height, gestational age and duration of surgery among groups ($P > 0.05$).

The percentages of successful spinal anesthesia at different doses of bupivacaine with 2.5 μg sufentanil in the four groups were showed in Figure 1. Logistic regression plots were drawn for success of spinal anesthesia in Figure 2. The 0.5 and 0.95 y-intercepts were used to calculate the ED_{50} and ED_{95} of intrathecal bupivacaine for both plots. The ED_{50} and ED_{95} of intrathecal bupivacaine coadministered with 2.5 μg sufentanil were 5.67 mg (95% confidence interval [*CI*]: 5.20–6.10 mg) and 8.82 mg (95% *CI*: 8.14–9.87 mg) respectively.

Thirty-eight cases in Group 4 mg, 26 cases in Group 6 mg, 5 cases in Group 8 mg required pidural 2% lidocaine supplements. Means of supplements volume of 2% lidocaine were higher in Group 4 mg than in the other three groups ($P < 0.05$) [Table 2]. The incidence of hypotension and the dose of phenylephrine administered were higher in Group 8 mg and Group 10 mg than in Group 6 mg and Group 4 mg ($P < 0.05$) [Table 2]. There were no significant differences among groups in the incidence of nausea, vomiting, shivering, headache and backache [Table 2]. The lowest blood pressures during the period from intrathecal drug administration to fetal delivery were significantly lower in Group 8 mg and Group 10 mg than in Group 6 mg and Group 4 mg [Figure 3].

Table 1: Demographic data and duration of surgery

Indices	Group 4 mg	Group 6 mg	Group 8 mg	Group 10 mg
Age (year)	30 ± 3	29 ± 4	30 ± 4	31 ± 4
Height (cm)	158.0 ± 6.8	160.0 ± 7.2	159.0 ± 7.4	158.0 ± 6.9
Weight (kg)	74.5 ± 7.3	75.0 ± 6.9	72.2 ± 5.9	72.8 ± 7.6
Gestational age (week)	36.2 ± 0.6	35.7 ± 0.5	36.8 ± 0.8	36.4 ± 0.6
Duration of surgery (minute)	39.4 ± 4.3	41.5 ± 5.2	40.3 ± 5.4	38.8 ± 3.8

All values were shown as mean ± SD. There were no significant differences among groups. SD: Standard deviation.

Satisfaction of the operation condition assessed by surgeon was poorer in Group 4 mg than other three groups ($P < 0.05$) [Table 3]. No significant differences in patient's satisfaction

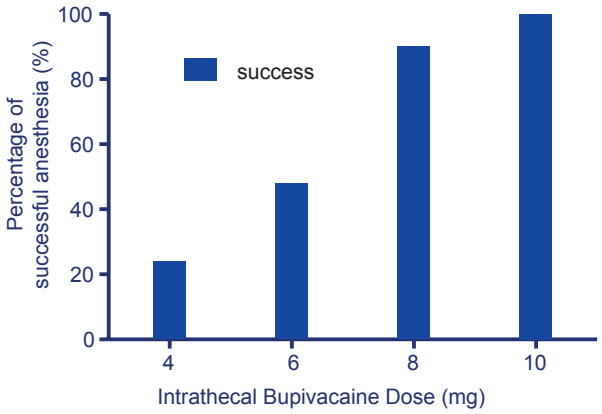

Figure 1: Success of anesthesia at different doses of intrathecal bupivacaine.

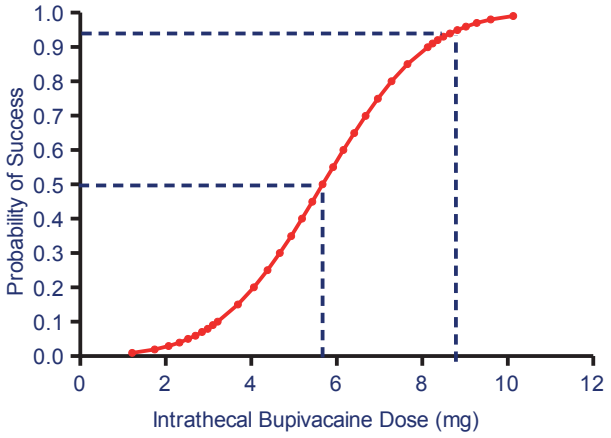

Figure 2: Logistic regression plot of the probability of successful spinal anesthesia versus intrathecal bupivacaine dose. Probability of 0.5 and 0.95 was used for deriving the ED_{50} and ED_{95} of intrathecal bupivacaine to achieve successful spinal anesthesia for C-section.

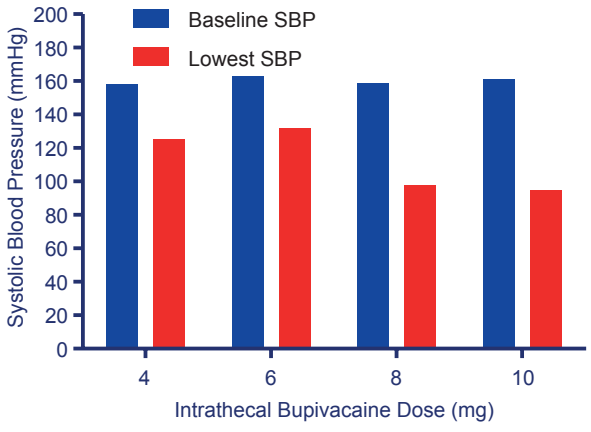

Figure 3: The systolic blood pressure (SBP) at baseline and the lowest SBP during the period from intrathecal drug administration to fetal delivery in the four groups.

among groups were found ($P > 0.05$) [Table 4]. There were no significant differences among groups in Apgar scores at 1, 5 minutes and fetal umbilical artery blood gas analysis [Table 5].

Table 2: Anesthetic characteristics and adverse effects

	Group 4 mg	Group 6 mg	Group 8 mg	Group 10 mg
Sensory level (to pinprick) (at 10 minutes after intrathecal drug administration)*	T8 (T12-T6)	T6 (T8-T4)	T4 (T6-T3)	T3 (T4-T2)
Patients requiring epidural lidocaine (*n*)*	38	26	5	0
2% lidocaine used (ml)	14.4 ± 3.8	3.0 ± 0.8†	1.2 ± 0.3†	0†
Phenylephrine used (μg)	8.5 ± 3.1	6.2 ± 2.5	25.4 ± 7.5†‡	30.3 ± 8.3†‡
Hypotension (*n* (%))	8 (16)	5 (10)	21 (40)	34 (68)
Nausea and vomiting (*n* (%))*	6 (12)	3 (6)	4 (8)	7 (14)
Shivering (*n* (%))	8 (16)	6 (12)	6 (12)	5 (10)
Headache (*n* (%))	0	0	0	0
Backache (*n* (%))	3 (6)	2 (4)	2 (4)	4 (8)

Data were shown as mean ± SD or median (range) or patient's number (percentage). *$P < 0.05$, compared among groups; †$P < 0.05$, compared with group 4 mg; ‡$P < 0.05$, compared with group 6 mg. SD: Standard deviation.

Table 3: Satisfaction to operation condition assessed by surgeon

	Group 4 mg	Group 6 mg	Group 8 mg	Group 10 mg
Good	24	45*	48*	48*
Moderate	18	4*	2*	2*
Poor	8	1*	0*	0*

Data were presented as patient's number. *$P < 0.05$, compared with Group 4 mg.

Table 4: Patient's satisfaction with anesthesia

	Group 4 mg	Group 6 mg	Group 8 mg	Group 10 mg
Good	42	46	45	40
Moderate	3	3	3	4
Poor	5	1	2	6

Data were presented as patient's number. No significant differences among groups.

Table 5: Apgar scores at 1, 5 minutes and fetal umbilical artery blood pH

	Group 4 mg	Group 6 mg	Group 8 mg	Group 10 mg
1 minute apgar score	9 (5-10)	9 (4-10)	9 (5-10)	9 (4-10)
5 minutes apgar score	9 (8-10)	9 (9-10)	9 (7-10)	9 (8-10)
Umbilical artery pH	7.32 ± 0.05	7.36 ± 0.08	7.34 ± 0.04	7.36 ± 0.06

Data were presented as median (range), except umbilical artery pH, which was presented as mean ± SD. No significant differences among groups, SD: Standard deviation.

Discussion

The present study found that the ED_{50} and ED_{95} of intrathecal bupivacaine for cesarean section in severely preeclamptic patients were 5.67 mg (95% *CI*: 5.20–6.10 mg) and 8.82 mg (95% *CI*: 8.14–9.87 mg) respectively, when co-administered with intrathecal 2.5 μg sufentanil.

Although a historically pervasive belief that spinal anesthesia in patients with severe preeclampsia causes severe hypotension, consequently decreases utero-placental perfusion, limited the widespread use of spinal anesthesia in these patients, spinal anesthesia has gained acceptance as an alternative to epidural anesthesia for these patients due to the findings from some studies that preeclampsia patients experienced a lower incidence of hypotension and required smaller doses of vasopressors compared with the normotensive patients after the initiation of spinal anesthesia.[3,18-20] Moreover, spinal anesthesia affords shorter onset of anesthesia and more reliable anesthesia than epidural anesthesia, suggesting that spinal anesthesia could have an advantage in emergency cesarean section in severe preeclampsia patients. However, in general severely preeclampsia patients experience more severe hypotension after spinal anesthesia than after epidural anesthesia although the spinal-induced hypotension in severe preeclampsia patients typically easily treated and short-lived.[21] Therefore, reducing or avoiding spinal-induced hypotension is a focus task while we choose spinal anesthesia for patients with severe preeclampsia. A recent study suggested that lower intrathecal bupivacaine (7.5 mg vs. 10 mg, when coadministered with fentanyl 20 μg) offered more stable hemodynamic level in severely preeclamptic patients,[7] then a reduction of intrathecal local anesthetic was advised to reduce spinal-induced hypotension for these patients.[3] However, an ideal effective dose of intrathecal bupivacaine for cesarean section in severe preeclampsia patients has not been determined and quantified so far. To our best knowledge, the present study is the first time to determine the ED_{50} and ED_{95} of intrathecal bupivacaine with sufentanil for cesarean section in severely preeclamptic patients with large subjects using dose-response methodology.

The ED_{50} of intrathecal hyperbaric bupivacaine for cesarean section in severe preeclampsia patients was determined as 5.67 mg in the present study, which is inconsistent with the result of Tyagi *et al*.'s study[2] that suggested the ED_{50} of intrathecal hyperbaric bupivacaine was 4.7 mg for severe preeclampsia patients. The difference in ED_{50} of intrathecal bupivacaine for severe preeclampsia patients between our study and Tyagi's study might be because of that as follows: (1) methodologies used are different. Our study was performed with a dose-response method, whereas Tyagi's study was performed with up-down sequential method. As we know, different methods for determining ED_{50} would produce a difference in results. In addition, using the up-and-down method to determine the ED_{50} of

drugs can observe only one point of the dose-response curve, which is the ED_{50}. Whereas using dose-response method can provide more information with whole points from ED_1 to ED_{99}, including ED_{50} and ED_{95}. Moreover, the dose-response method with Logistic regression analysis used for determining ED_{50} of ED_{95} has been validated elsewhere in the anesthetic literature.[15,22] (2) The criteria of successful spinal anesthesia are different. Successful spinal anesthesia was defined as a T4 level of sensory block with modified Bromage score of 1 or 2 was achieved within 15 minutes of intrathecal injection. Whereas in our present study, the successful spinal anesthesia was defined as a bilateral T6 sensory block level to pinprick was achieved within 10 minutes of the intrathecal drug administration, and/or no additional epidural analgesia was required during operation. Criteria of successful spinal anesthesia of our study were stricter than that of Tyagi's study, which could result in fewer cases of successful spinal anesthesia in our study. (3) Type of opioid adjuvant to intrathecal bupivacaine is different between the studies. Our study chose sufentanil as the adjuvant, whereas Tyagi's study used fentanyl. Intrathecal both fentanyl and sufentanil could reduce the dose requirement of intrathecal local anesthetics for cesarean section.[6,11,23] Sufentanil has a higher affinity to opioid receptors, a less cephalad spread and a much higher analgesic potency than fentanyl.[10] Several studies[11,24-26] using intrathecal sufentanil with local anesthetics have been reported, of which the dose of sufentanil ranged from 2.5 μg to 20 μg. Considering few studies have been conducted to investigate spinal anesthesia with sufentanil and bupivacaine in severe preeclampsia patients, and these patients usually have dramatic pathophysiological changes which might have an effect on pharmacodynamics of intrathecal opioids, so we chose 2.5 μg sufentanil, the lowest of reported doses, for the present study. Whether a higher dose of intrathecal sufentanil could result in the lower requirement of intrathecal bupivacaine for cesarean section in patients with severe preeclampsia needs to be further studied.

We noticed that the rate of successful spinal anesthesia was higher in Group 10 mg than in Group 8 mg, higher in Group 8 mg than in Group 6 mg and higher in Group 6 mg than in Group 4 mg, moreover in the groups with higher dose of bupivacaine the level of patients' satisfaction to operation was also higher than in the groups with lower dose of bupivacaine, suggesting that higher dose of intrathecal bupivacaine, higher rate of successful spinal anesthesia, which is in agreement with most of previous investigations.[2,15,22,27,28] It is well-accepted that the ideal dose of intrathecal anesthetic agents for cesarean section is essentially a balance between the conflicting demands of avoiding patient discomfort and avoiding adverse maternal effects such as hypotension.[15,22] Our present study demonstrated that the incidence of hypotension was higher in Group 10 mg than in Group 8 mg, higher in Group 8 mg than in Group 6 mg and Group 4 mg (no difference between Group 6 mg and Group 4 mg), suggesting that although increasing the dose of intrathecal bupivacaine could increase the successful spinal anesthesia rate, higher doses of intrathecal bupivacaine resulted in higher incidence of maternal hypotension. And other investigations[15,22] did not demonstrate that increasing dose of bupivacaine resulted in a greater incidence of hypotension probably due to insufficient powered sample size. Our study with a large sample size is sufficient powered to detect a difference in maternal hypotension among groups. Hence, we could say our conclusion that increasing intrathecal dose of bupivacaine would result in a higher incidence of hypotension in patients with severe preeclampsia is reliable.

Although our study determined quantifiably the ED_{50} and ED_{95} of intrathecal bupivacaine co-administered with 2.5 μg sufentanil for cesarean section in patients with severe preeclampsia, it is impossible to determine the ideal dose for every patient due to the large individual variations in response to intrathecal anesthetics. It was recommended by Carvalho *et al*.[15] That when using a low dose of bupivacaine, close to the ED_{50}, combined spinal epidural technique should be considered to allow epidural supplementation for patients with inadequate analgesia. Based on present study, intrathecal 6 mg of bupivacaine could be a relatively ideal dose for cesarean section for severe preeclampsia with a lower incidence of hypotension, when considering the balance of the conflicting demands of avoiding patient discomfort and avoiding adverse effect.

Our results showed that SBP in Group 8 mg and Group 10 mg was significantly lower than in Group 6 mg and Group 4 mg, but that did not result in fetal acidemia, because the risk of fetal acidemia depends on the severity and duration of the hypotensive episode.

In summary, the present study demonstrated that the ED_{50} and ED_{95} of intrathecal bupivacaine for cesarean section in severely preeclamptic patients were 5.67 mg and 8.82 mg, when coadministered with intrathecal 2.5 μg sufentanil using CSEA. In addition, the lower dose of intrathecal bupivacaine for these patients could result in a decrease of incidence of maternal hypotension and a decrease of vasopressor requirements. Further studies with a wider range of bupivacaine dose using the dose-response method to determine the ED_{50} and ED_{95} of intrathecal bupivacaine for cesarean section in patients with severe preeclampsia are needed.

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