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Original Article

Influence of prophylactic phenylephrine infusion on dose requirements of intrathecal hyperbaric bupivacaine during spinal anesthesia in cesarean sections: a pilot study

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Abstract: Background: Phenylephrine has been widely used in C-sections. However, it has been reported to decrease the spread of intrathecal local anesthetics. This present study aimed to observe the effects of prophylactic phenylephrine infusion on dose requirements of intrathecal hyperbaric bupivacaine during spinal anesthesia in cesarean sections. Methods: Based on receiving or not receiving phenylephrine infusion, fifty patients were enrolled and allocated into Group P or Group S (n = 25). Spinal anesthesia was performed with 10 mg of intrathecal bupivacaine. Effective anesthesia was defined as a T_6 or higher sensory block (lost to pinprick) level achieved in 10 minutes after spinal injection, with no patient complaints of pain during surgery. The primary outcome was the percentage of effective anesthesia. Characteristics of spinal anesthesia and side effects were also studied. Results: Percentage of effective anesthesia was lower in Group P than in Group S (68% vs. 92%, $P = 0.034$). Block level was lower in Group P than in Group S (T_6 vs. T_4, $P < 0.001$). Onset time to T_5 was slower in Group P than in Group S (7.8 ± 1.4 vs. 6.3 ± 1.5, $P = 0.003$). Incidence of hypotension was significantly lower in Group P than in Group S (8% vs. 40%, $P = 0.008$). Conclusion: A higher dose of intrathecal bupivacaine is needed when phenylephrine infusion is chosen to prevent spinal-induced hypotension in cesarean sections under spinal anesthesia or CSEA.

Keywords: Phenylephrine, cesarean section, intrathecal, bupivacaine, spinal

Introduction

Spinal anesthesia has been used worldwide in patients undergoing lower abdominal surgery, including C-sections. It has been associated with high incidence of hypotension, however. Phenylephrine has been suggested as the first choice to manage spinal-induced hypotension, due to its effectiveness and better fetal acid-base status [1, 2]. However, studies have found that phenylephrine infusion can decrease the rostral spread of spinal anesthesia [3, 4]. Therefore, it was hypothesized that a higher dose of intrathecal bupivacaine would be needed in cesarean sections with phenylephrine infusion to prevent spinal-induced hypotension.

Methods

Study subjects and grouping

This study obtained approval from the Institutional Ethics Committee of Jiaxing University Affiliated Women and Children Hospital. Written informed consent was obtained from all patients. A total of 50 subjects with ASA status I or II and single pregnancies requiring elective cesarean sections were enrolled. Patients with a body mass index (BMI) greater than 30 kg/m^2, twin pregnancies, intrauterine fetal distress, chronic hypertension, coagulation abnormality, platelet count less than $75\times10^9/L$, local infection or sepsis, and history of cardiac, respiratory, renal, or hepatic failure were excluded from the current study. Patients, with or without phenylephrine infusion, were

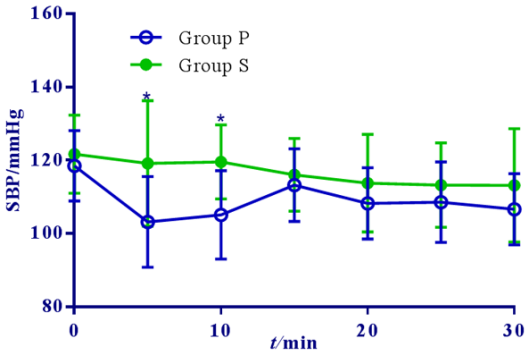

Figure 1. Comparison of SBP in the 30 minutes after induction of SA. The SBP was obviously more stable in Group P than in Group S, $^{*}P < 0.05$.

randomized allocated into Group P and Group S, using a simple randomized list generated by Microsoft Excel.

Spinal anesthesia management

Standard monitoring, including non-invasive blood pressure (NIBP), heart rate (HR), oxygen saturation (SpO2), and electrocardiogram (ECG), was applied and recorded. The average value of three systolic blood pressure (SBP) recordings taken at 1-minute intervals was regarded as baseline. Combined spinal-epidural anesthesia (CSEA) was performed at L_{3-4} interspace with the patient in a left lateral position, using a needle-through-needle technique. Patients received a routine dose of intrathecal 10 mg of hyperbaric bupivacaine, with a total volume of 2.5 mL injected over 15 seconds. An epidural catheter was then inserted 3-4 cm cephalad into the epidural space. Patients were then in a supine position with a 15° left tilt. At the time of spinal injection, patients received 15 mL/h (50 mcg/min) phenylephrine infusion (10 mg in 50 mL of syringe) or the same volume of saline infusion in Group P or Group S, respectively. Co-loading of 500 mL of Ringer's solution was also administered.

Management of hemodynamics

Hypotension was defined as a decrease in SBP over 20% of baseline. It was treated with 50 μg of phenylephrine and repeated if necessary. Hypertension was defined as an increase in SBP over 20% of baseline. The infusion was stopped and restarted if the SBP decreased to the normal range. A heart rate below 55 bpm was regarded as bradycardia. If accompanied with hypotension, it was treated with 0.5 mg of intravenous atropine. If not accompanied with hypotension, the infusion was stopped and restarted when the heart rate was over 55 bpm. The number of effective anesthesia, sensory block level at 10 minutes after spinal injection, and time to T_6 block level in effective anesthesia were studied. Newborn outcomes were evaluated by umbilical artery blood gas analysis.

Measurements

The primary outcome was the percentage of effective anesthesia in the two groups. Secondary outcomes included characterization of spinal anesthesia and side effects. Effective anesthesia was defined as a T_5 or higher sensory block (lost to pinprick) level achieved in 10 minutes after spinal injection, with no patient complaints of pain during surgery [5-7]. Otherwise, it was considered as an effective anesthesia. Epidural of 5 mL of 2% lidocaine was then given to help the induction or rescue the intraoperative pain. Lidocaine was repeated at 5-minute intervals if necessary. Patient demographics, obstetrics, and surgical data were studied. The number of effective anesthesia, sensory block level at 10 minutes after spinal injection, and times to T_6 block level in effective anesthesia were studied. Side effects and newborn outcomes were evaluated by umbilical artery blood gas analysis and 1-minute Apgar scores were studied.

Statistical analysis

Patient demographics, obstetrics, and surgical data are present as mean ± SD and were analyzed using Student's t-test. Bromage scores and incidence of side effects are presented as numbers (percentage) and were analyzed using Chi-squared test. Sensory block level, supplement of epidural lidocaine, cesarean history, and 1-minute Apgar scores are presented as median (range). They were analyzed using Mann-Whitney U-test. Times to first predelivery SBP dropping more than 20% of baseline were analyzed using the log-rank test with Kaplan-Meier analysis. Changes in SBP in the first thirty minutes after spinal anesthesia were analyzed by repeated measures ANOVA. Statistical analysis was performed with GraphPad Prism 5 (version 5.01). Statistical significance is defined as $P < 0.05$ (two-sided).

Table 1. Patient demographics, obstetrics, and surgical data

Issues	Group P (n = 25)	Group S (n = 25)	*P*-value
Age (y)	28 ± 3	29 ± 3	0.41*
Height (cm)	159 ± 3	160 ± 3	0.42*
Weight (kg)	75 ± 4	73 ± 4	0.84*
Gestational age (week)	39 ± 1	39 ± 1	0.60*
Duration of surgery (min)	45 ± 7	47 ± 7	0.41*
Induction-delivery (min)	15 ± 4	15 ± 3	0.86*
Uterine incision-delivery (s)	62 ± 18	65 ± 20	0.72*
Cesarean history	1 (0, 1)	1 (0, 1)	0.59†
Umbilical artery pH	7.27 ± 0.04	7.26 ± 0.06	0.224*

Data are presented as mean ± SD or median (range). *Student's t test, †Mann-Whitney U test.

Table 2. Characteristics of spinal anesthesia

Issues	Group P	Group S	*P*-value
Effective anesthesia	17 (68)	23 (92)	0.034#
Block level (10 min after induction of SA)	T_6 (T_4, T_8)	T_4 (T_3, T_7)	< 0.001†
Onset time to T_5 in effective case	7.8 ± 1.4	6.3 ± 1.5	0.003*
Bromage score 2/3 in effective case	2/15	4/19	0.622#
Supplement of lidocaine	10 ml (5-10 ml)	10 ml (10-10 ml)	0.533†

Data are presented as mean ± SD or median (range). #Chi-square test, *Student's t test, †Mann-Whitney U test.

Table 3. Side effects and newborn outcomes

Issues	Group P	Group S	*P*-value
Hypotension	2 (8)	10 (40)	0.008#
Hypertension	2 (8)	0 (0)	0.149#
Nausea and vomiting	2 (8)	8 (34)	0.034#
Bradycardia	2 (8)	0 (0)	0.149#
Shivering	6 (24)	4 (16)	0.480
1 min Apgar score	9 (7, 9)	9 (7, 9)	0.621†
Umbilical artery pH	7.27 ± 0.04	7.26 ± 0.06	0.224*

Data are presented as mean ± SD, Median (range) or number (percentage). #Chi-square test, *Student t test, †Mann-Whitney U test.

Results

Comparison of general conditions between the two groups

All patients completed the study and were included in the final analysis, as shown in **Figure 1**. There were no significant differences in characteristics of maternal demographics, obstetrics, and surgical data (**Table 1**, P > 0.05).

Comparison of characteristics of spinal anesthesia between the two groups

The percentage of effective anesthesia was lower in Group P than in Group S (68% vs. 92%, P = 0.034). Block level was lower in Group P than in Group S (T_6 vs. T_4, P < 0.001). Onset time to T_5 was slower in Group P than in Group S (7.8 ± 1.4 vs. 6.3 ± 1.5, P = 0.003). There were no significant differences in Bromage scores and supplements of epidural lidocaine (**Table 2**, P > 0.05).

Comparison of side effects and newborn outcomes between the two groups

Incidence of hypotension was significantly lower in Group P than in Group S (8% vs. 40%, P = 0.008). Incidence of nausea and vomiting was significantly lower in Group P than in Group S (8% vs. 34%, P = 0.034) (**Table 3**). There were no significant differences in other side effects and newborn outcomes.

Comparison of the hemodynamics between the two groups

Baseline SBP and SBP in the thirty minutes after spinal anesthesia in each group are shown in **Figure 1**. SBP was higher in Group P than in Group S, *P* < 0.05. Times to first predelivery SBP dropping more than 20% of baseline was significantly delayed in Group P than in Group S, *P* = 0.005 (**Figure 2**).

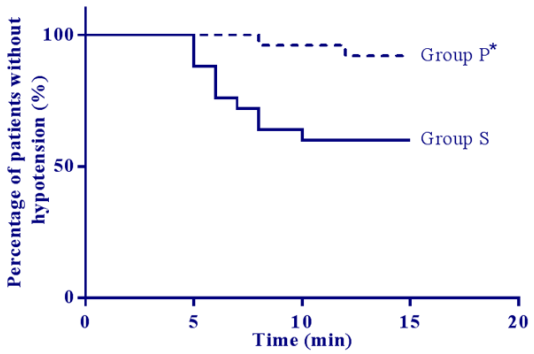

Figure 2. Times to first predelivery SBP dropped more than 20% of baseline were analyzed using the log-rank test with Kaplan-Meier analysis, $^{*}P = 0.005$.

Discussion

The present study found that incidence of effective anesthesia was lower with phenylephrine infusion than without phenylephrine infusion (68% vs. 92%, $P = 0.034$). These results suggest that a higher dose of intrathecal hyperbaric bupivacaine may be needed when using prophylactic infusion of phenylephrine to prevent spinal-induced hypotension.

This study found that there was an average of two segments lower of sensory block levels with phenylephrine infusion than without phenylephrine infusion, in the 10 minutes after induction of spinal anesthesia. The present results were similar to two previous studies conducted by Cooper and his coleagues [3, 4]. They demonstrated that intravenous phenylephrine can decrease rostral spread of spinal local anesthetics in pregnancies, compared with intravenous ephedrine. However, the clinical significance of this finding remains unclear. As phenylephrine has been widely used in obstetrician anesthesia practices, it is necessary to attest the dose requirements of intrathecal local anesthetics (that may be different) for cesarean sections when prophylactic phenylephrine infusion is applied. Possible mechanisms of this phenomenon may be as follows. 1) Phenylephrine infusions make epidural veins constricted and then offset the effects of epidural vein engorgement which can increase the spread of intrathecal local anesthetics in pregnant woman; and 2) Phenylephrine infusions may delay the onset of sensory block. In this study, the onset time to T_6 level of effective anesthesia was delayed about 1.5 minutes in Group P. Phenylephrine infusions increasing the volume of lumbar cerebrospinal fluid would be a reasonable explanation of this delay. Incidence of hypotension, nausea, and vomiting was obviously improved by phenylephrine infusion in the current study ($P = 0.008$, 0.034). It was clear that the hemodynamics (SBP) were more stable with phenylephrine infusions (**Figure 1**). Moreover, time to experience hypotension was delayed with phenylephrine infusion. Therefore, using phenylephrine infusion to prevent spinal-induced hypotension in cesarean sections under spinal anesthesia or CSEA is strongly recommended.

There were some limitations to the present study. The dose-response was not determined for this current study. Future studies should focus on this. There are many factors which can affect the spread of spinal anesthesia. Although attention was paid to many issues, including maternal position during performing anesthesia, speed of injection of intrathecal solution, gravity of intrathecal solution, and the total volume of study solution, this study ignored the weight of newborns. This omission may have affected the results.

In summary, this study suggests that a higher dose of intrathecal bupivacaine is needed when choosing phenylephrine infusions to prevent spinal-induced hypotension in cesarean sections under spinal anesthesia or CSEA. Dose-response studies of intrathecal bupivacaine are needed to confirm the results of this study.

Disclosure of conflict of interest

None.

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