นิพนธ์ต้นฉบับ

Intravenous ephedrine infusion for prophylaxis of hypotension during spinal anesthesia for cesarean section

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Abstract:
Background: *In general, most parturients with no contraindications receive spinal anesthesia for cesarean section. The incidence of hypotension is high and this leads to decreased uteroplacental blood flow with possible fetal acidemia.*

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Objectives: *To study the efficacy of ephedrine infusion prophylaxis for hypotension associated with spinal anesthesia for elective cesarean sections compared with traditional preloading. The outcomes of this study were the incidence of hypotension during the operation, neonatal outcomes and the side effects of ephedrine.*
Method: *With a concealed randomized study, 96 parturients were allocated into two groups, the study group received ephedrine 18 mg (3 ml) added to 100 ml normal saline, while the control group received 3 ml of normal saline instead of ephedrine intravenous continuous infusion given over 10 minutes. All patients had preloading fluid with lactated Ringer's solution 20 ml/kg 10 minutes before being injected with 0.5% hyperbaric bupivacaine mixed with preservative free morphine at intervertebral lumbar space 3-4 or 4-5.*
Results: *The incidence of hypotension was 93.8% in the control group and 85.4% in the study group (p = 0.181). Neonatal outcomes, as measured by Apgar scores at 1 and 5 minutes, were the same in each group. Other side effects such as reactive hypertension, palpitations, tachycardia and headaches were not different between the groups.*
Conclusion: *The results of the study indicate that there is no significant advantage from using ephedrine infusion (18 mg) for the prophylaxis of hypotension during spinal anesthesia for cesarean sections, compared with standard treatment.*

Key words: *cesarean section, hypotension, intravenous ephedrine infusion, spinal anesthesia*

บทคัดย่อ:

ผู้ป่วยที่มาผ่าท้องทำคลอดได้รับการระงับความรู้สึกโดยวิธีฉีดยาชาเข้าช่องน้ำไขสันหลัง พบอุบัติการณ์ความดันเลือดต่ำได้สูง ทำให้การไหลเวียนเลือดไปรกลดลง ส่งผลให้เกิดปัญหาแก่ทารกได้
วัตถุประสงค์: *ศึกษาเปรียบเทียบประสิทธิภาพอุบัติการณ์ความดันเลือดต่ำ คะแนน Apgar ของทารกแรกคลอด และผลข้างเคียงของยา ephedrine แบบหยดต่อเนื่องทางหลอดเลือดดำกับกลุ่มควบคุมที่ได้รับการรักษาตามมาตรฐานหลังการฉีดยาชาเข้าช่องน้ำไขสันหลัง*
ระเบียบวิธีวิจัย: *ผู้ป่วยที่มาผ่าท้องทำคลอด 96 ราย แบ่งเป็น 2 กลุ่มด้วยวิธีสุ่ม กลุ่มศึกษาได้รับ ephedrine 18 มก. (3 ซีซี) ผสมในน้ำเกลือนอร์มอล 100 ซีซี กลุ่มควบคุมได้รับน้ำเกลือนอร์มอล (ยาหลอก) 3 ซีซี ผสมในน้ำเกลือนอร์มอล 100 ซีซี หยดต่อเนื่องทางหลอดเลือดดำภายใน 10 นาที ผู้ป่วยทุกรายได้รับสารน้ำ Lactated Ringer's solution 20 ซีซีต่อน้ำหนักก่อน จึงฉีดยาชา 0.5% hyperbaric bupivacaine ในตำแหน่ง intervertebral space L3-4 หรือ L4-5*
ผลการศึกษา: *อุบัติการณ์ความดันเลือดต่ำในกลุ่มควบคุมและกลุ่มศึกษา คือ ร้อยละ 93.8 และ 85.4 (p = 0.181) ตามลำดับ คะแนน Apgar นาทีที่ 1 และ 5 ใกล้เคียงกัน ผลข้างเคียง เช่น reactive hypertension, ใจสั่น หัวใจเต้นเร็ว และปวดศีรษะทั้ง 2 กลุ่มไม่ต่างกัน*

สรุป: *ผลการศึกษาพบว่า อุบัติการณ์ความดันเลือดต่ำโดยเปรียบเทียบระหว่างกลุ่มที่ให้ยา ephedrine แบบหยดต่อเนื่องทางหลอดเลือดดำและกลุ่มควบคุม ไม่แตกต่างกัน*

คำสำคัญ: *การผ่าท้องคลอด, การระงับความรู้สึกโดยวิธีฉีดยาชาเข้าช่องน้ำไขสันหลัง, ยา ephedrine แบบหยดต่อเนื่องทางหลอดเลือดดำ, อุบัติการณ์ความดันเลือดต่ำ*

Introduction

Spinal anesthesia is accepted as the appropriate choice of anesthesia for cesarean section. The main advantages being that failed intubation, aspiration of gastric content and drug induced depression in the mother or fetus associated with general anesthesia are usually avoided, although there are major concerns about sympathetic block with associated hypotension and potential harmful maternal and fetal effects. The incidence of hypotension in pregnant patients after spinal anesthesia is reported to be as high as to 80%.[1] This can have adverse effects on the neonatal acid-base status through placental hypoperfusion resulting in acidosis and poor Apgar scores.[2] In addition, the hypotension can lead to unpleasant maternal symptoms[3] such as nausea, vomiting and faintness.[2] The incidence and severity of hypotension depend on the height of the block, the position of the parturient, and whether prophylactic stratagems were taken to avoid such hypotension. Although non-pharmacological techniques including, lateral uterine displacement, intravenous pre-hydration (preload) and physical methods to improve venous return such as leg elevation and lower limb wrapping are currently suggested to prevent or minimize hypotension, there is no established ideal technique.[4]

Prehydration is the one of stratagems used to prevent hypotension by intravenous administration of 1-2 L of fluid, 15-20 minutes before the spinal block to fill capacitance dilated vessels.

Ephedrine has been the vasopressor of choice in the management of hypotension induced by spinal or epidural blockade in obstetric anesthesia[5] because it increases blood pressure with minimal effects on the uteroplacental blood flow[1] and does not adversely affect the fetus.[5] Ephedrine can be administered by an i.v. infusion pump or by i.v. or i.m. boluses. The goal of this present study was to evaluate the efficacy of prophylactic ephedrine infusion for the prevention of hypotension associated with spinal anesthesia for cesarean section.

Materials and methods

This study was conducted at Songklanagarind Hospital, Hat Yai, Songkhla. Approval from the Institutional Ethics Committee and patient consent were obtained. Ninety-six parturients with normal pregnancies scheduled for a cesarean section under spinal anesthesia were allocated by a computer generated random number and assigned blind to one of two groups. Two groups of 48 parturients each used a sealed envelope technique according to the

drug used for the maintenance of their blood pressure. The control or prehydration group received a 3 ml placebo in 100 ml of 0.9% saline and the ephedrine infusion group received ephedrine 18 mg (3 ml) in 100 ml of 0.9% saline. The inclusion criteria were as follows: elective surgery, American Society of Anesthesiologists (ASA) class I-II, age between 18-40 years, term singleton pregnancy. Exclusion criteria included high risk pregnancy (pregnancy induced hypertension, placenta previa, abruption placenta), twin pregnancy, underlying medical conditions (hypertension, heart disease, cerebrovascular disease), allergy to bupivacaine or ephedrine, contraindication for spinal anesthesia and fetal distress.

All patients were assigned nil through the mouth nil per os (NPO) after midnight on the day before delivery, and they received oral ranitidine 150 mg and metoclopramide 10 mg as premedication at bedtime. An intravenous infusion of lactated Ringer's solution (LRS) 2 ml/kg/hr was begun at 7.00 am on the day of surgery. The parturients were given ranitidine 150 mg orally 1 hour before the start of anesthesia and 30 ml of 0.3 Molar sodium citrate orally on arrival at the operating room. Baseline measurements of noninvasive blood pressure (NIBP) and heart rate (HR) were recorded with the patient in the supine position. Intravenous fluid preloading with 20 ml/kg of LRS was infused within 10-15 minutes then decreased to 10 ml/kg/hr until the end of the operation. Spinal anesthesia was administered, with the parturients in the lateral decubitus position, via a 27-gauge Quincke-type needle inserted with side port cephalad, at the L3/4 or L4/5 interspace into the subarachnoid space. After establishing a free flow of clear cerebrospinal fluid, heavy bupivacaine 0.5%, 2 ml with preservative-free morphine 0.2 mg with a total volume of 2.2 ml was injected in patients over 150 cm tall. The volume of bupivacaine was decreased to 1.8 ml if the patient's height was 141-150 cm and the volume was further decreased by 0.2 ml for every 5 cm of a decrease in the patient's height. After an intrathecal injection, patients moved into a supine position and achieved left uterine displacement. The level of spinal anesthesia was assured to at least the L1 level through verification by loss of pinprick sensation. Then, patients received the study infusion. Surgery was allowed to proceed when the upper sensory level of block reached at least T6.

The study infusion, in which parturients, anesthesiologists and nurse anesthetists were blinded, was administered for 10 minutes. After the intrathecal injection, systolic blood pressure (SBP) and HR were recorded every 1 minute for 20 minutes and then every 5 minutes until the operation ended. Hypotension was defined as a SBP fall of ≥20% from the baseline or an absolute value of <90 mmHg of SBP and severe hypotension was defined as a SBP fall of ≥30% from the baseline value. Upward and downward titration and temporary interruption and restarting of the study infusion were used after every 1 minute measurement of SBP to maintain the SBP between the hypotension values and baseline values. Rescue boluses of ephedrine 6 mg were given if severe hypotension or resistant to fluid therapy developed. The study infusion was stopped if the SBP increased to more than 120% of the baseline values, which was defined as reactive hypertension.

The supplemental and total doses of ephedrine required in all patients, spinal injection to delivery time and uterine incision to delivery time, were

recorded. Blood loss was assessed. The total volume of intravenous fluid was recorded. Events of nausea or vomiting, the maximal level of anesthesia and Apgar scores at 1 and 5 minutes were recorded. After delivery, synthetic oxytocin (Syntocinon) 10 units in 1000 ml of LRS was infused at the rate of 10 ml/kg/min. Methylergonovine maleate (Methergin) 0.2 mg was slowly infused as needed for better uterine contraction.

Statistics

The sample size of 96 parturients in this study was calculated from an 80% power to detect a decrease in the proportion of patients developing hypotension from 70%[6] to 35% at a significance level of 0.05. The baseline and non-time-varying variables were compared across the 2 groups using tabulation and the chi-square or Fisher exact test for discrete variables and the t-test or rank sum test as appropriate for continuous variables. Time-varying continuous variables were compared graphically across the groups using means and 95% confidence intervals at each time point and statistically using maximum likelihood random intercept regression modeling.

Results

Baseline demographics were generally comparable between the two groups. Although parturient demographics were similar among the groups, the American Society of Anesthesiologists (ASA) classification was significantly different (p = 0.024). There were no significant differences among the groups in the maximum level of anesthesia, the amount of preloading fluid, the amount of intraopera-

Table 1 Characteristics of patients receiving prehydration or ephedrine infusion

	Prehydration group (N = 48)	Ephedrine infusion group (N = 48)	P-value
Age (year)	31.4±4.3	31.1±4.8	0.966
Body weight (kg)	70.27±9.82	67.15±11.77	0.331
Height (cm)	156.35±4.84	155.60±6.26	0.057
Gestational age (wk)	38 (38, 39)	38 (38, 39)	0.457
ASA class			0.024
1	16 (33.33%)	27 (56.25%)	
2	32 (66.67%)	21 (43.75%)	
Level of anesthesia			0.835
$\geq T_4$	29 (63.42%)	28 (58.34%)	
$< T_4$	19 (38.58%)	20 (41.66%)	
Preloading fluid (mL)	1,318.8±199.6	1,252.1±235.2	0.1377
Total fluid (mL)	2,365.6±496.3	2,364.6±592.8	0.9926
Estimate blood loss (mL)	489.6±178.6	493.8 ±184.1	0.9106

Data are mean ± SD or median (range) or number (percentage)

tive fluid administration or blood loss (Table 1). The time from the spinal injection to the infusion drug, the time from the spinal injection to child birth, the time from uterine incision to child birth and the amount of synthetic oxytocin or methylergonovine maleate were not significantly different between the two groups. The time taken from the spinal anesthesia to the end of surgery in the study group was, however, significantly prolonged compared to the prehydration group (p = 0.016).

The incidence of hypotension and the amount of intraoperative supplementary ephedrine were not significantly different between groups (p = 0.181 and p = 0.196, respectively) (Table 2). In both groups there was no significant difference of serious complications, such as reactive hypertension, nausea, vomiting, palpitations, tachycardia and headaches. High spinal anesthesia, defined as the maximum level of spinal anesthesia at T1, was not significant between groups. There was no arrhythmia in either group but both did show tachycardia (Table 3). Neonatal outcomes expressed as Apgar scores, at 1 and 5 minutes,

Table 2 Incidence of hypotension and rescue ephedrine dose administered

	Prehydration group (N = 48)	Ephedrine Infusion group (N = 48)	P-value
Incidence of hypotension*	45 (93.8)	41 (85.4)	0.181
Rescue ephedrine dose administered (mg)**	0 (0-30)	6 (0-48)	0.196

* number (percentage) ** median (range)

Table 3 Incidence of adverse effects

	Prehydration group n (%)	Ephedrine infusion group n (%)	P-value
Reactive hypertension	0 (0)	3 (6.25)	0.078
Nausea vomiting	12 (25.00)	16 (33.33)	0.369
Palpitation	3 (6.25)	5 (10.42)	0.460
Arrhythmia/tachycardia	5 (10.42)	5 (10.42)	1.000
Headache	2 (4.17)	1 (2.08)	0.557

Table 4 Neonatal status at birth

	Prehydration group (N = 48) n (%)	Ephedrine infusion group (N = 48) n (%)	P-value
Apgar score at 1 min			0.372
7	1 (2)	0 (0)	
8	4 (8)	9 (18.75)	
9	41 (85)	37 (77.08)	
10	2 (4)	2 (4.17)	
Apgar score at 5 min			0.547
7	0 (0)	1 (2.08)	
8	1 (2.08)	0 (0)	
9	4 (8.33)	5 (10.42)	
10	43 (89.58)	42 (87.50)	

were similar among both groups (Table 4).

The patients in the ephedrine infusion group maintained significantly higher blood pressures than those in the pre-hydration group ($p < 0.001$) (Figure 1). The mean systolic blood pressure of the ephedrine infusion group was 128.7 mmHg, which was higher than the pre-hydration group at 122.3 mmHg. No significant difference in heart rate was noted between the groups ($p = 0.191$), although the mean heart rate of the ephedrine infusion group, at 94.7 beats per minute, was higher than the prehydration group at 91.6 beats per minute (Figure 2).

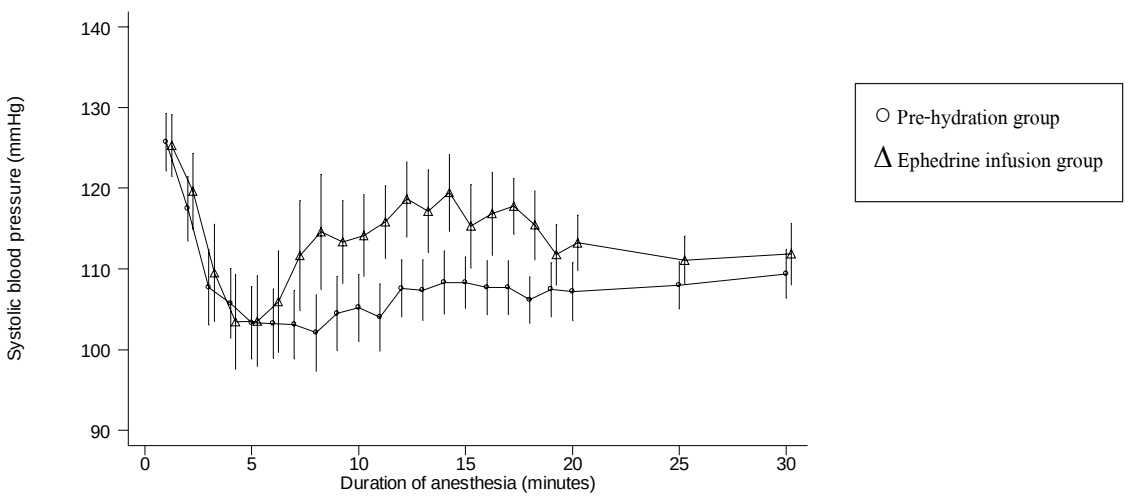

Figure 1 Changes in systolic pressure in patients

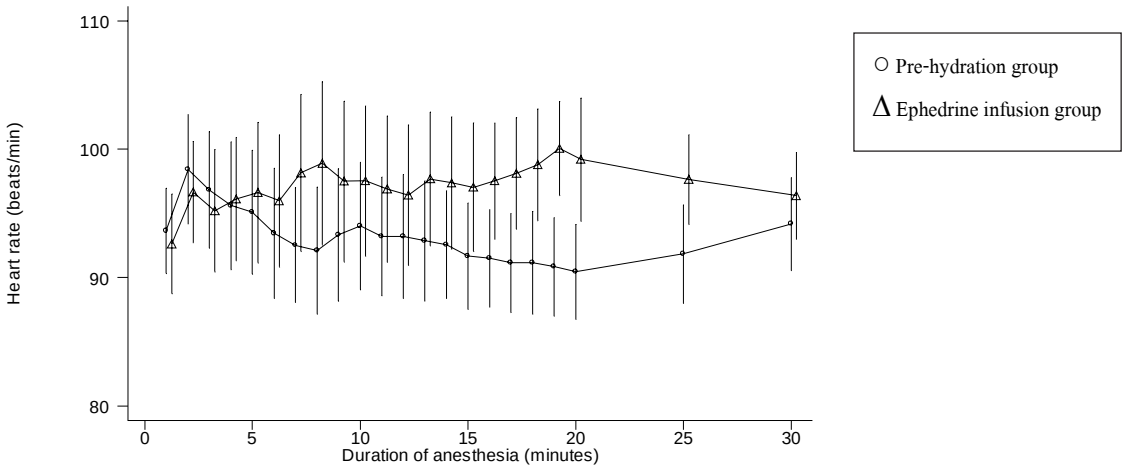

Figure 2 Changes in mean heart rate

Discussion

The difference in proportion of hypotension between the two groups in our study was not statistically significant, which may be due to the insufficiency of the ephedrine infusion dose and the infusion rate. In our study we chose 18 mg of ephedrine, based on the findings of an earlier study by Loetwiriyakun et al.[7] at Songklanagarind Hospital, which found that 18 mg of ephedrine was the optimum intravenous bolus dose for the prevention of hypotension during spinal anesthesia for cesarean sections. It was also within the range recommended by Simon et al.[8], who found that a single bolus of ephedrine with a dose of either 15 or 20 mg significantly decreased the incidence of maternal hypotension as compared with 10 mg bolus of ephedrine. Some studies used a higher dose, such as the one by Desalu and Kushimo[9] that used a prophylactic infusion of 30 mg ephedrine which they found more effective than crystalloid pre-hydration and Nqan Kee et al.[10], found that the lowest effective dose of ephedrine to reduce the incidence of hypotension was 30 mg infusion for 30 seconds. In our study, we chose 18 mg of ephedrine because it has not been done before using this amount of ephedrine compared with crystalloid prehydration.

The use of ephedrine as a continuous titrated infusion has been found to be associated with better control of arterial pressure and with fewer maternal side-effects compared with intermittent intravenous bolus doses[3] or intramuscular administration.[11] In our study we infused 18 mg of ephedrine in 10 minutes, which took time to reach a therapeutic level, after the sympathetic system had been blocked by the spinal anesthesia. So this method of prophylaxis by infusion alone would not be suitable for a prompt rapid onset requirement.

The disadvantage of using ephedrine is an increase in heart rate and contractility, which is likely to increase myocardial oxygen demand. Marked increases in heart rate may be associated with

unpleasant palpitations, atrial and ventricular ectopic beats and tachyarrhythmias.[12] In our study there were no differences in reactive hypertension and tachycardia between our two groups and no patients from either group required treatment with antihypertensive drugs. This was also the finding of the Loughrey et al.[3], who found that 12 mg of ephedrine intravenously did not cause rebound hypertension and tachycardia. Desalu and Kushimo[9] found that the incidence of hypertension and tachycardia were not significantly different between the prehydration and ephedrine groups. Nausea and vomiting, which are the most frequent side effects of maternal hypotension, occurred in similar proportion in both our groups.

We did not detect a difference in the parameter of neonatal wellbeing in the two groups of this study. Although, ephedrine crosses the placenta and affects the fetal and neonatal heart rates, it does not affect neonatal outcome.[13] Ramin et al.[14] found a 40% rate of fetal acidemia, defined as an umbilical artery pH 7.20, in women receiving prophylactic ephedrine. A meta-analysis showed that umbilical arterial pH is significantly lower with the use of ephedrine compared with phenylephrine.[15] But Chan et al.[16] compared ephedrine infusion and fluid preload for the prevention of spinal hypotension during cesarean section, and found the hypotension rate was lower and the umbilical pH was higher in the ephedrine groups. Mercier et al.[17] reported a 63% incidence of fetal acidosis with a prophylactic intravenous infusion of ephedrine in parturients receiving spinal anesthesia during cesarean sections. However, the Apgar scores at 1 and 5 minutes were never lower than 7 in their study. As the result of their study, the use of an Apgar score is a good index of immediate survival[18], which is also suitable for use in our environment.

A post-hoc power analysis, in which the incidence of hypotension in the control group was set, more correctly at 93.8%, indicated that a sample size of 48 patients per group would have sufficient power (80%) to detect a significant difference between groups only if the incidence of hypotension in the ephedrine infusion group was ≤70%. Thus, there is insufficient evidence from this study for such a reduction in the incidence of hypotension in the ephedrine infusion group.

Conclusion

The use of 18 mg of ephedrine infusion prophylaxis for hypotension during spinal anesthesia for cesarean sections may be insufficient for the maintenance of normal blood pressure compared with volume preloaded patients. The inconclusive findings to date indicate further studies are needed.

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