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Original Article

Prophylactic Intravenous Bolus Ephedrine for Elective Caesarean Section Under Spinal Anesthesia

ผลการให้ยาอีฟีดรีนในหญิงตั้งครรภ์ที่ผ่าตัดคลอดภายใต้การระงับความรู้สึกเฉพาะที่

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ABSTRACT

Objective : To evaluate the efficacy and optimal dose of prophylactic intravenous ephedrine for the prevention of maternal hypotension associated with spinal anesthesia for Caesarean section.

Methods : After patients had received an intravenous preload of 15 ml/kg of lactated Ringer's solution, spinal anesthesia was administered in the right lateral decubitus position with 0.5% hyperbaric bupivacaine 1.8 ml combined with 200 mcg morphine. A total of 90 patients were randomized to receive a simultaneous 2 ml bolus intravenously of either 0.9% saline (Group C, n = 30), ephedrine 5 mg (Group E-5, n = 30) or ephedrine 10 mg (Group E-10, n = 30). Further rescue boluses of ephedrine 5 mg were given if systolic arterial pressure tall below 90 mmHg, greater than 20% below baseline or if symptoms suggestive of hypotension were reported.

Results : There were no significant differences in the incidence of hypotension (53.67% vs 33.33%, 36.63%) $p > 0.05$, nausea or vomiting between groups. Rebound hypertension were not observed and there were no significant differences in Apgar scores. Less rescue doses of ephedrine were required in Group E-5, E-10 compare with the control group (0.83 ± 1.23 vs 1.73 ± 1.81, 0.70 ± 1.19 vs 1.73 ± 1.81, $p < 0.05$).

Conclusion : Intravenous bolus ephedrine 5, 10 mg could not prevent or reduce incidence of hypo-

tension in parturients received spinal anesthesia for cesarean delivery but less rescue doses of ephedrine were required in Group E-5, E-10 compare with the control group.

Keywords : spinal anesthesia, ephedrine, hypotension, caesarean section

บทคัดย่อ

วัตถุประสงค์ เพื่อศึกษาผลการให้ยาอีฟีดรีนในหญิงตั้งครรภ์ที่ผ่าตัดคลอดภายใต้การระงับความรู้สึกเฉพาะที่

วิธีการศึกษา เป็นการศึกษา double-blind randomized controlled ระหว่าง มกราคม 2549 - เมษายน 2550 ในหญิงตั้งครรภ์ 90 คน แบ่งเป็น 3 กลุ่ม กลุ่มละ 30 คน ภายหลังจากให้สารน้ำ lactate Ringer's 15 มล./กก. และให้การระงับความรู้สึก โดยใช้เทคนิค spinal ในท่าตะแคงขวาด้วยยา 0.5% hyperbaric bupivacaine 1.8 ซีซี ร่วมกับ morphine 200 ไมโครกรัม กลุ่มควบคุมได้รับ normal saline 2 ซีซี กลุ่ม E-5 ได้รับอีฟีดรีน 5 มิลลิกรัมขนาด 2 ซีซี กลุ่ม E-10 ได้รับอีฟีดรีน 10 มิลลิกรัม ขนาด 2 ซีซี ให้อีฟีดรีน 5 มิลลิกรัม เมื่อความดันโลหิตต่ำกว่า 90 มม.ปรอท หรือลดลงต่ำกว่า 20% หรือมีอาการคลื่นไส้อาเจียน

ผลการศึกษา ไม่พบการลดลงของอุบัติการณ์ความดันโลหิตต่ำในกลุ่มศึกษาอย่างมีนัยสำคัญ (53.67% vs 33.33%, 36.63%) $p > 0.05$ ไม่พบความแตกต่างในค่า Apgar score ในทารกแรกคลอดทั้ง 3 กลุ่ม รวมทั้งไม่พบภาวะความดันโลหิตสูงในกลุ่มศึกษา

สรุป การให้ยาอีฟีดรีนในขนาด 5 หรือ 10 มิลลิกรัม ไม่ลดอุบัติการณ์เกิดความดันโลหิตต่ำในหญิงตั้งครรภ์ที่ได้รับการระงับความรู้สึกเฉพาะที่ชนิด spinal เพื่อผ่าตัดคลอด และขนาดยาดังกล่าวไม่มีผลต่อ Apgar score ในทารกแรกคลอด

Introduction

Spinal anesthesia is very popular for cesarean delivery because it offers a fast, profound and symmetrical sensory and motor block of high quality. However, despite crystalloid or colloid preloading, hypotension remains a common complication,[1-3] with a varied reported incidence of 8-70%.[1,4] The dose of intrathecal local anesthesia and to a lesser extent the co-administration of intrathecal opoid, appear to play a key role on the incidence of hypotension.[5] This in addition to technique of prophylaxis, can have a substantial effect on incidence, severity and duration of hypotension. Maternal hypotension has been shown to produce adverse effects on the neonatal outcome.[6] In recent study, found a very low incidence of hypotension in well hydrated patients receiving a small dose spinal with hyperbaric bupivacaine and the administration of 5 mg ephedrine before turning to supine position.[1] However, the benefit of the prophylactic ephedrine dose in that study was unclear. The prophylactic administration of ephedrine by intramuscular route is very controversy because it, 's systemic absorption and peak effect is difficult to predict, thus possibly resulting in rebound hypertension.[7-8] The intravenous route may be more effective and controllable but despite large doses, the incidence of hypotension was still high and cause reactive hypertension.[9] In another study, increasing

doses of ephedrine were associated with decreasing umbilical artery pH in patients having spinal and epidural anesthesia.[10]

In a prospective randomized double blind study, we examined the effects of two different dose of ephedrine given as a prophylactic intravenous bolus compared with a control group on the incidence of hypotension following low dose spinal anesthesia for Caesarean delivery.

Methods

Following hospital Ethics Committee approval and informed patient consent. We studied 90 term and periterm patients presenting for elective Caesarean section during January 2006 to April 2007. Exclusion criteria included patients with pre-eclampsia, a history of essential hypertension or those with contraindication to spinal anesthesia.

Standard monitoring included noninvasive arterial pressure, electrocardiogram and pulse oximetry. Baseline measurements of systolic arterial pressure, using a cuff on the right arm and heart rate were recorded in the operation room. After an intravenous preload of lactated Ringer's solution 15 ml/kg over 15 min, the patients received an intrathecal injection of 0.5% hyperbaric bupivacaine 1.8 ml combined with morphine 200 mcg via 25 G quincke needle at the L 3-4 in the right lateral decubitus position. Patients received the study drug simultaneously with the intrathecal injection. The patients were then placed supine with a 15^0 left lateral tilt and given 8 L of oxygen via a face mask with bag. Patients were randomized to receive a bolus of 0.9% saline intravenous (Group C), ephedrine 5 mg (Group E-5) or ephedrine 10 mg (Group E-10) in 2 ml of solution prepared by another anesthetic nurse not in that operation room. Randomization was performed by labeling pieces of paper, identified group, in opaque envelop (n = 90). All observers were blinded to the study solution. The height of block was recorded as the highest dermatome with loss of fine pinprick sensation prior to skin incision. Systolic arterial pressure was recorded every 1 min until delivery then 3 min after that. Patients were asked to report any symptoms of nausea or vomiting.

Maternal hypotension was defined as a reduction in systolic pressure greater than 20% from baseline or a reading below 90 mmHg. Tachycardia was defined as an increation in heart rate greater than 20% from baseline. Further rescue boluses of ephedrine 5 mg were given if hypotension occurred or if symptoms suggestive of hypotension were reported, without waiting for a recorded fall of arterial pressure. Addition doses of ephedrine were given based on clinical response. All patients received oxytocin 10 units following delivery and Apgar scores were noted at 1 and 5 min. An estimate of sample size was reference to study of J.P.R. Loughrey, et al.[11] The individual group size of at least $n = 20$ was designed to have an 80% probability of detecting a reduction in the incidence of hypotension in either study group of greater than 50%, assuming a baseline incidence of 75%, $p < 0.05$ was considered significant. One-way analysis of variance was used to compare parametric data. Chi-square was used for frequency data.

Results

All groups were comparable in weight, height, sensory block height achieved. There was no significant differences in the incidence of hypotension between groups. There were no differences between the groups with respect to patient demographics and sensory block height.

There was a significantly higher incidence of hypotension in Group C compared with Group E-5, E-10 (53.67% vs 33.33%, 36.63%) $p > 0.05$. Less rescue doses of ephedrine were required in Group E-5, E-10 compare with the control group (0.83 ± 1.23 vs 1.73 ± 1.81, 0.70 ± 1.19 vs 1.73 ± 1.81, $p < 0.05$). No differences were found between groups

Table 1 Demographics and spinal block data

	C (n = 30)	E-5 (n = 30)	E-10 (n = 30)	p
Age (year) (mean ± SD)	30.03 (4.86)	32.5 (3.655)	31.73 (7.643)	0.228
Weight (kg)	66.47 (10.143)	69.27 (10.67)	69.37 (10.532)	0.478
Height (cm)	155.9 (4.31)	157.8 (6.008)	156.83 (6.17)	0.421
Sensory block height, median (range)	T5 (T4-6)	T5 (T4-5)	T5 (T4-6)	

C : control group, E-5 : ephedrine 5 mg group, E-10 : ephedrine 10 mg group. Value expressed as mean (± standard deviation)

Table 2 Maternal outcome

	C (n = 30)	E-5 (n = 30)	E-10 (n = 30)	p
Patients have hypotension	16	10	11	0.241
Patients require rescue ephedrine	18	11	11	0.110
Rescue ephedrine doses (5 mg) administered	1.73 (1.818)	0.83 (1.234)	0.70 (1.119)	0.012*
Patients have nausea	16	8	10	0.086
Patients have hypertension	0	0	0	
Patients have tachycardia	1	2	3	0.585
Time consume for sensory block at T10	102.33 (14.247)	99.33 (9.977)	89.33 (10.807)	<0.001*

C : control group, E-5 : ephedrine 5 mg group, E-10 : ephedrine 10 mg group Value expressed as mean (± standard deviation)

Table 3 Neonatal outcome and side effects

	C (n = 30)	E-5 (n = 30)	E-10 (n = 30)	p
Apcar score < 8				
At 1 min	0	0	0	
At 5 min	0	0	0	
Itching	11	11	7	0.443
Nausea or vomiting	16	8	10	0.086

C : control group, E-5 : ephedrine 5 mg group, E-10 : ephedrine 10 mg group Value expressed as number of patients

with regard to tachycardia, hypertension. Rebound hypertension was not observed in the groups receiving prophylactic ephedrine.

There were no significant differences in the incidence of maternal symptoms of nausea or vomiting. In 3 patients ephedrine was administered because of nausea without any evidence of hypotension (two in Group C and one in Group E-5) and there were no significant differences in the incidence of maternal symptoms of Itching due to neuaxial morphine. No differences were observed in neonatal well being by Apgar score < 8. This study was founded that time consumed for sensory block decreased to T10 level was significant different between groups.

Discussion

In parturients undergoing cesarean delivery with regional anesthesia, the preservation of maternal normotension is a desirable goal for maternal and fetal well being. Datta et al.[6] demonstrated that the avoidance of maternal hypotension, through the prompt administration of intravenous ephedrine, resulted in a significant reduction in maternal nausea, emesis and an infant acid-base status within normal parameters and equal to infants whose mothers did not experience hypotension. This demonstration suggested that prophylactic use of ephedrine may prevent maternal hypotension.

The expansion of intravascular volume, the use of left lateral uterine displacement and the administration of vasoactive medications have been utilized with variable success in preventing maternal hypotension. Although the effectiveness of intravascular volume preloading in preventing maternal hypotension has been questioned,[12-13] the simultaneous use with ephedrine appears to improve cardiac output and may promote cardiovascular stability.[14] We chose to include a 15 mL/kg bolus of lactated Ringers immediately before the administration of spinal anesthesia in our study, as larger amounts have been observed to have no additional effect on maternal hemodynamics or ephedrine requirements in a similar

population.[15] For ethical reasons we did not included a group without prehydration. In addition, although left uterine displacement alone does not prevent hypotension, it has been demonstrated to reduce the incidence of maternal hypotension and improve neonatal blood gas and Apgar evaluations,[16-17] consequently we utilized this our standard positioning technique.

The 5 mg dose of ephedrine for both prophylaxis and treatment was chosen because that is the usual clinical practice. The dose of bupivacaine we used is at the lower end of the range used by others. Our clinical practice is normally to use small doses because of the smaller stature of Asian women compared with Western women. We added morphine 200 mcg to the intrathecal local anesthetic, which is our usual practice to improve surgical anesthesia. In our study patients were given "rescue" ephedrine as soon as hypotension occurred and the total dose of ephedrine given was different among groups. We found no difference in heart rate among groups. This could be explained by both by the effect of "rescue" ephedrine and by baroreceptor-mediated reflex increases in heart rate in patients who became hypotensive. Olsen, et al.[18] concluded that although mean arterial blood pressure tended to decrease less in parturients who had received prophylactic intravenous ephedrine (0.15 mg/kg bolus dose plus 0.4 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}), this did not adequately prevent hypotension. King and Rosen[19] reported that neither ephedrine bolus doses alone nor an ephedrine bolus dose plus an infusion (10 mg bolus $\pm$ 10 mg infused over 10 min) decreased the incidence of hypotension, which remained at 60%. Tsen, et al.[20] similarly found that a 10 mg bolus of ephedrine did not prevent hypotension (70% incidence). Ngan Kee, et al.[21] Reported an 80-85% incidence of hypotension despite prophylactic 10 or 20 mg bolus doses of ephedrine.

Only parturients randomized to receive the largest ephedrine bolus dose (30 mg) experienced a lower incidence of hypotension (35%) but this dose caused frequent reactive hypertension. Therefore, this technique may not be suitable in some patients, for example those with cardiovascular or cerebrovascular disease. Although Kang, et al[22] reported the successful use of 10 mg of ephedrine in maintaining SBP greater than 70% of baseline pressures, this was given as an intravenous infusion (10 mg of ephedrine/500 mL of lactated Ringer's) over the first 2 minutes after spinal anesthesia, with manual titration thereafter to maintain systolic blood pressure. In addition, although Shearer, et al[23] concluded that an IV 10 mg dose of ephedrine given at the time of regional local anesthetic injection for cesarean delivery resulted in hypotension (SBP < 100 mmHg) as commonly as a smaller control group (69% vs. 70%, respectively), a number of factors could have obscured their results ; the patients were not randomized to ephedrine versus control groups, received epidural, spinal or combined spinal-epidural anesthetics, were positioned in the sitting or lateral position and received different IV preload amounts.

The principal finding of this study is that a 5 or 10 mg bolus of intravenous ephedrine, given at the time of spinal medication dosing and immediately after a 15 mL/kg preload with lactated Ringers solution, did not prevent hypotension. The most likely

reasons for this finding are two-fold. Foremost is the unpredictable nature of spinal anesthesia-induced hypotension, which makes its prevention with ephedrine or even other measures, difficult. Secondly, an inadequate ephedrine dose may have been used. In terms of the ephedrine dose, 10 mg bolus doses of ephedrine have been effective in the restoration[22] and maintenance of BP after spinal anesthesia ; however, multiple doses are often required in quick succession.[24] This finding would suggest that response to a given ephedrine dose is highly individualized and agrees with the suggestion by Rout, et al,[2] that the prevention of spinal induced hypotension may require a sustained increase in cardiac output. This most likely explains why ephedrine given in the form of a titrated infusion has been successful in preventing severe hypotension.[25] The observation that none of the patients in the ephedrine group experienced hypertension or tachycardia may also suggest that larger bolus doses could have been used. Despite the 54% incidence of hypotension in saline groups, all neonatal Apgar scores were normal. Although umbilical blood gases would have been helpful as a measure of neonatal well being, the association between maternal hypotension and adverse neonatal base status has already been well documented.[26]

In summary, this study demonstrated 5 or 10 mg of intravenous ephedrine given simultaneously with the dosing of spinal anesthesia and immediately after a 15 mL/kg lactated Ringers fluid bolus, does not diminish the incidence of hypotension in parturients undergoing cesarean delivery. This consistent with the findings of previous studies in which smaller dose were not effective, although the incidence of hypotension was reduced to 36.6% in patients who received ephedrine 10 mg compare with the control rate of 53.33%. The incidence of hypotension in this study was lower than others study be due to smaller dose of bupivacaine and optimized prehydration. The incidence of maternal symptoms of nausea or vomiting were no significant differences between groups and the same as Apgar scores, this result was same as other study. The recent study of the dose response meta-analysis was stronger for hypertension than for hypotension. These findings suggest that the use of larger doses of ephedrine does not completely eliminate hypotension but causes reactive hypertension and a minor decrease in umbilical arterial pH.[27] It would be of interest to determine whether different timing of the bolus, injection over a longer period of time or injection in divided doses would reduce the incidences of hypotension and hypertension.

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