

## Original Research Article

# Ephedrine versus phenylephrine: effects on fetal acid-base status during spinal anesthesia for elective cesarean delivery

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## ABSTRACT

**Background:** During elective caesarean sections, post-spinal hypotension is a common problem. Prevention of this complication by sympathomimetic agents is of potential clinical significance. The objective of this study was to compare and evaluate the effects of ephedrine and phenylephrine on the fetal outcome when used in the treatment of maternal hypotension during spinal block in elective caesarean section.

**Methods:** After fulfilling the inclusion criteria, hundred patients were enrolled in this study and were randomly allocated into two groups of fifty each. According to their group, patients received either ephedrine 6 mg (group E) or phenylephrine 75µg (group P) as vasopressor. For spinal anaesthesia lumbar puncture was done in sitting position and 12.5mg, 0.5% hyperbaric bupivacaine was given intra-theccally to every patient. Throughout surgery, maternal and neonatal complications were controlled and recorded. During the study, Apgar scores on the 1<sup>st</sup> and 5<sup>th</sup> minutes, and blood gases of the umbilical cord blood were evaluated.

**Results:** Ephedrine and phenylephrine were used in the mean doses of 6.72±1.97mg and 91.5±31.38µg respectively. There was no significant difference observed in total number of boluses used in treating post-spinal hypotension. The difference in the first- and fifth-minute Apgar scores was statistically insignificant between the group E and group P. There was a statistically significant difference observed in SaO<sub>2</sub> and base excess in arterial gas sample between two studied groups. Similarly, a significant difference was observed in PCO<sub>2</sub> of umbilical venous sample between two studied groups. However, none of the neonates had the true fetal acidosis.

**Conclusions:** Intravenous phenylephrine 75µg and ephedrine 6 mg offer a comparable hypotensive control without any significant complication for mother or her fetus in elective caesarean section.

**Keywords:** Apgar score, caesarean section, Ephedrine, Elective lower abdominal surgery, Phenylephrine, Post spinal hypotension

## INTRODUCTION

During spinal anesthesia, hypotension is a common complication in obstetric patients and its prevalence in cesarean section is about 50-90%.<sup>1-3</sup> Post spinal hypotension can result in adverse effects for both mother and infant.<sup>4-5</sup> It may reduce placental perfusion and result

in fetal acidosis and neurological injury.<sup>1-3</sup> For the prevention of hypotension, several techniques have been proposed.<sup>1-3,6</sup> Currently the vasoconstrictor agents which are being recommended and used for controlling hypotension are phenylephrine and ephedrine, but still nowadays the choice of vasopressor is being debated.<sup>7</sup> Recently, there have been concerns regarding the use of

ephedrine because of complications such as supraventricular tachycardia, tachyphylaxis, and the probability of fetal acidosis.<sup>1-3,6,8-10</sup> Ephedrine produces its effect by releasing norepinephrine from nerve endings in the autonomous nervous system. It is a non-catecholamine sympathomimetic agent that stimulates alpha- and beta-adrenergic receptors directly and predominantly indirectly. Despite the lack of confirmation of its superiority over other vasopressors, ephedrine traditionally is the vasopressor of choice in obstetric anesthesia.<sup>11,12</sup> Phenylephrine is a strong alpha-agonist of sympathetic receptors. It reduces the incidence of maternal nausea and vomiting as well as fetal acidosis, but it may result into maternal bradycardia and decreased cardiac output. Therefore, the use of phenylephrine, especially for prophylaxis of hypotension, is uncommon.<sup>1,3,10,13</sup>

Results of several trials suggest that phenylephrine may have similar efficacy to ephedrine for preventing and treating hypotension during spinal anesthesia.<sup>14-17</sup> However, the relative effects of these vasopressors on neonatal outcome are unclear, and there is need for a large randomized controlled trial with emphasis on important neonatal outcomes.<sup>18,19</sup> The aim of the study was to examine whether ephedrine and phenylephrine were different in their effect of adverse neonatal outcome, evaluate the side effects of this therapy, and to study fetal changes using Apgar scores and arterial and venous umbilical cord blood gases.<sup>2</sup>

## METHODS

The present randomized, observational study was performed in a maternity hospital which is one of the associated hospitals of a government medical college from January 2014 to November 2016. Prior to the study, all patients signed an informed consent. In total, 100 full term singleton pregnant women with ASA class II undergoing elective cesarean section were recruited. The sample size was calculated using the incidence of hypotension as the primary outcome. The study subjects were in the age range of 24 to 35 years, height 152-167 cm, weight 63-85 kg and gestational age 36-39 weeks and were a candidate of elective lower abdominal surgery. Patients with classic contraindications to subarachnoid block, pre-existing systemic disease, known fetal abnormalities, pre-eclampsia and known allergy to test drugs were excluded from the study. Using the simple random method, the patients were randomly allocated into two groups (n=45 each), namely group E and group P.

- Group E (n=50): Ephedrine 6mg in 1ml as intravenous (IV) bolus,
- Group P (n=50): Phenylephrine 75µg in 1 ml as IV bolus.

Patients with 8-hours fast did not receive premedication. Standard monitoring was established in the operating

room, women rested in the supine position with left uterine displacement, and baseline blood pressure, SpO<sub>2</sub> (peripheral capillary oxygen saturation) and HR (heart rate) were measured and recorded. Then, two 18-gauge intravenous cannulas were sited. Each patient received a 10mL/kg IV infusion of Ringer's solution for 15 minutes before spinal anesthesia. After the completion of fluid infusions, all patients received spinal anesthesia in a sitting position from L3-4 or L4-5 interspaces using a 25-gauge Quincke needle with 12.5mg bupivacaine 0.5%. The total drug volume was 2.5mL. Immediately after spinal anesthesia, all patients were positioned in the supine position with left uterine displacement. The operation began after the sensory block at dermatome T4. Oxygen was administered at the rate of 5 lit/min by a face mask until the umbilical cord was clamped. Oxytocine 10 units in 5% dextrose in Ringer's solution was administered after the clamping of the cord. Blood pressure was controlled every 2 minutes after spinal anesthesia until delivery and then every 5 minutes throughout the operation. Moreover, HR and SpO<sub>2</sub> were controlled throughout anesthesia. Sensory block was monitored to obtain a T4-5 level of anesthesia. After delivery and clamping of the umbilical cord, 1mL of blood was drawn from the umbilical artery for neonatal blood gas analysis. Any decrease of about 20% from baseline in BP after spinal anesthesia was treated with 75µg phenylephrine (if associated with tachycardia) or 6 mg ephedrine otherwise. Bradycardia (maternal HR<50 beats/min) was treated with 0.5mg atropine if it was not associated with hypotension. The incidence of hypotension, maximal hypotension, duration of hypotension, total dose of injected vasopressors, and neonatal outcome parameters (first-and fifth-minute Apgar scores by neonatologist and PH of the umbilical artery) were recorded. Other collected data included the duration of operation and anesthesia (time of sensory block), umbilical cord blood gases which includes pH, PO<sub>2</sub>, PCO<sub>2</sub>, SaO<sub>2</sub> and base excess. Two surgeons were responsible for the operations. An anesthesiologist was responsible for the anesthesia and patient monitoring, and the other anesthesiologist and an assistant were responsible for recording patient information and completing the questionnaires.

## Statistical analysis

Data were analyzed using descriptive statistical methods (mean±SD), frequency, and percentage. Mean difference tests for independent samples were used for quantitative variables and chi-squared test or Fisher's exact test for qualitative variables. All data were analyzed using the SPSS software (version 16.0) and P<0.05 were considered statistically significant. The present study is approved by the ethics committee of the college. Written informed consent was obtained from the patients.

## RESULTS

At the end of the study, the data for 100 patients were collected (50 patients in group E and 50 patients in the group P). There was no significant difference in patients' demographic data between the groups (Table 1).

**Table 1: Maternal characteristics.**

General characteristics	Group E (n=50)	Group P (n=50)	P
Age (years)	28.4±2.61	27.7±2.45	0.12
Range	24-35	24-34	
Weight (kg)	75.08±5.72	73.40±5.79	0.14
Range	65-86	63-85	
Height (cm)	160.2±3.11	159.7±4.14	0.446
Range	155-167	152-167	
<b>Gestational age</b>			
36-37 weeks	24	25	0.536
n (%)	48	50	
38-39 wweeks	26	25	0.536
n (%)	52	50	
Mean± SD	37.6±1.14	37.4±1.11	

Values expressed as Mean± SD, \*p<0.05 is significant.

The mean age of patients in group E was 28.4±2.61 years and 27.7±2.45 years in group P. The mean weight in group E and group P respectively was 75.08±5.72 kg and 73.40±5.79 kg. There was no significant difference in patients' duration of operation and anesthesia, dermatomal sensory level, and duration of sensory block (Table 2).

**Table 2: Anesthetic and surgical parameters.**

Parameters	Group E (n = 30)	Group P (n = 30)	P value
Sensitive level at T4 (%)	4 (8%)	3 (6%)	0.287
Sensitive level at T5 (%)	26 (52%)	21 (42%)	
Sensitive level at T6 (%)	20 (40%)	26 (52%)	
Time from spinal block to delivery (min)	16.3±1.04	16.6±1.05	0.129
Range	15-18	15-18	
Time from skin incision to delivery time (min)	10.48±1.31	10.76±1.36	0.298
Range	8-13	8-13	
Vasopressor dose (mg)	6.72±1.97mg	91.5±31.38 µg	
Range	6-12	75-150	

Values expressed as Mean ± SD, \* p < 0.05.

Maternal baseline means arterial pressure (MAP) and HR values were not different between the two groups (P=0.9

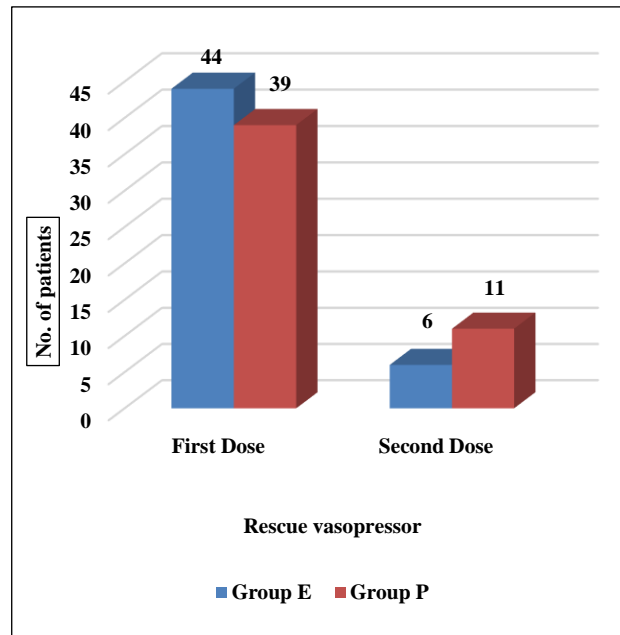
and P=0.8, respectively). Maternal side effects of spinal anesthesia and treatments are presented in (Table 3).

**Table 3: Baseline HR, systolic, diastolic and mean BP in all groups.**

Group parameter	Group E Mean±SD	Group P Mean±SD	P value
Heart rate	79.50±4.83	78.40±4.14	0.224
Systolic blood pressure	131.54±5.48	129.80±5.41	0.113
Diastolic blood pressure	78.16±3.63	77.26±3.63	0.218
Mean blood pressure	95.95±3.78	94.77±3.72	0.117

Values expressed as Mean ± SD, \* p <0.05.

In group P 78 percent parturient required a single dose of 75µg of phenylephrine while 22 percent patients needed second dose of vasopressor to maintain systolic blood pressure as shown in (Figure 1).



**Figure 1: Comparison of IV bolus doses of vasopressors required to treat hypotension.**

This use of vasopressor ephedrine at a dose of 6mg was respectively 88 percent and 12 percent in group E. The number of rescue doses required in both the groups was statistically insignificant (P<0.05: significant). Neonatal outcomes are shown in (Table 4 and 5).

There was a statistically significant difference observed in SaO<sub>2</sub> and base excess in arterial gas sample between two studied groups. Similarly, a significant difference was observed in pCO<sub>2</sub> of umbilical venous sample between two studied groups. However, the difference in first-and fifth-minute Apgar scores between babies of two studied groups was statistically insignificant.

**Table 4: Arterial and venous umbilical cord blood gases.**

Group parameter	Group E Mean±SD	Group P Mean±SD	P value	
Arterial	pH	7.27±0.13	7.30±0.12	0.157
	PO <sub>2</sub> (mmHg)	18.62±1.89	19.14±2.22	0.174
	PCO <sub>2</sub> (mmHg)	51.28±4.38	48.42±5.32	0.092
	SaO <sub>2</sub>	25.54±2.31	35.98±3.05	<0.001*
	Base excess (m Eq/l)	-1.37±2.75	1.21±2.48	<0.001*
Venous	pH	7.25±0.12	7.28±0.13	0.178
	PO <sub>2</sub> (mmHg)	32.72±4.91	31.06±3.97	0.067
	PCO <sub>2</sub> (mmHg)	45.18±3.44	39.28±3.15	<0.001*
	SaO <sub>2</sub>	41.74±4.31	42.32±3.90	0.497
	Base excess (m Eq/l)	-2.39±2.08	2.37±1.27	<0.001*

Values expressed as Mean ± SD, \* p < 0.05.

**Table 5: Neonatal outcomes of the two groups.**

Outcome	Group E	Group P	P value
Apgar in 1 <sup>st</sup> min	7.92	8.06	0.302
Apgar in 5 <sup>th</sup> min	9.49	9.56	0.462

## DISCUSSION

In this study, authors showed no significant differences between ephedrine and phenylephrine in maternal and neonatal outcomes, although the treatment with phenylephrine had neonates with higher arterial SaO<sub>2</sub>, and base excess than the ephedrine group and the difference was significant. There is no significant difference in umbilical cord arterial pH, pO<sub>2</sub>, pCO<sub>2</sub> between ephedrine and phenylephrine group. The parturient treated with ephedrine had neonates with lower pH both in umbilical arterial and venous samples although the difference was non-significant. These results were consistent with the systematic review performed by Lee A et al, and the meta-analysis performed by Lin FQ et al.<sup>18,20</sup> The reason for the difference in umbilical arterial pH values is that ephedrine crosses the placenta; therefore, it is possible that ephedrine may have a direct effect on the fetus that contributes to acidosis.<sup>8,18,21-22</sup> In spite of this, fetal clinical adverse effects caused by reduced fetal pH have not been demonstrated.<sup>23</sup> In present study none of the neonates had Apgar scores <7, so there was no difference in the risk of low Apgar scores at 1 min or at 5min (<7) between the ephedrine and phenylephrine groups.<sup>18,24</sup> The findings of present study are in agreement with other studies: women given phenylephrine had neonates with higher umbilical arterial pH values than those given ephedrine, although there is no risk for true fetal acidosis in none of groups.<sup>8,25</sup> The results of this study are in accordance with other previous studies, that showed that patients in the phenylephrine group were more likely than the ephedrine group to develop bradycardia.<sup>15-16,18,26</sup> The limitations of this study are that only uncomplicated and elective caesarean deliveries were included. In complicated and emergency

cases response of vasopressors may be different. One possible limitation is that the study was conducted in a single center.

## CONCLUSION

In conclusion, the superiority of the two vasopressors: ephedrine or phenylephrine, in treating spinal-induced intra-operative hypotension during cesarean sections, has been argued for years. In summary, present study supports the idea that ephedrine and phenylephrine have the same efficacy in treating hypotension after spinal anesthesia for caesarean section. The use of both the vasopressors was associated with better fetal acid-base status. Although the use of phenylephrine was associated with a little better fetal acid-base status compared to the use of ephedrine, but there were no differences on Apgar score values.

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