Original Article

Ephedrine versus Phenylephrine: Prevention of Hypotension during Spinal Anaesthesia for Cesarean Section and Effects on the Fetus

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Abstract

Background: *Hypotension during spinal anaesthesia for cesarean section is secondary to the sympathetic blockade and aorto-caval compression by the uterus and it can be deleterious to both the fetus and the mother. Ephedrine and phenylephrine improve venous return after sympathetic blockade during the spinal anaesthesia.*

Aim: *The aim of this study was to compare intravenous bolus doses of phenylephrine and ephedrine in preventing and treating hypotension in spinal anaesthesia for caesarean section and the effect of vasopressors on fetal outcome in terms of Apgar score.*

Materials and Methods: *Total 100 patients of ASA Grade I undergoing caesarean section under spinal anaesthesia with a normal singleton pregnancy beyond 37 weeks gestation was randomly allocated into two groups of 50 each. Group I received prophylactic bolus dose of ephedrine 10 mg IV at the time of intrathecal block with rescue boluses of 5 mg. Group II received prophylactic bolus dose of phenylephrine 100 ¼g IV at the time of intrathecal block with rescue boluses of 50 ¼g. Hemodynamic variables like blood pressure and heart rate was recorded every 2 minutes up to delivery of baby and then after every 5 minutes. Neonatal outcome was assessed using Apgar score at 1 and 5 minutes and neonatal umbilical cord blood pH Values.*

Results: *There was no difference found in managing hypotension between two groups. Incidence of bradycardia was higher in phenylephrine group. The differences in umbilical cord pH, Apgar score, and birth weight between two groups were found statistically insignificant.*

Conclusion: *Ephedrine and Phenylephrine are equally efficient in managing hypotension during spinal anesthesia for caesarean section. There was no difference between two vasopressors in the incidence of true fetal acidosis. Neonatal outcome remains equally good in both the groups.*

Keywords: *Ephedrine, fetal acidosis, hypotension, phenylephrine, spinal anaesthesia.*

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Introduction

Spinal anaesthesia has become one of the most acceptable anaesthetic techniques for caesarean section. Due to its rapid onset, intensity, symmetric sensory and motor block, it has been successfully used for caesarean section. Spinal anaesthesia has lower complications than that of general anaesthesia in both mother and foetus[1]. However, despite these advantages, hemodynamic complications, especially hypotension of the

mother, which is related to sympathetic blockade, is a common complication (up to 80% of pregnant patients), and has remained a major concern both for the mother and foetus[2]. Systolic hypotension higher than 20% to 30% of patient's baseline blood pressure can lead to maternal low perfusion pressure, manifested as nausea-vomiting, dizziness, low conscious and utero-placental hypo perfusion with fetal hypoxia and acidosis. Therefore, prevention and treatment of this complication, with special medical agents for optimal keeping of mother's blood pressure and foetal circulation has been an important issue for both anaesthesiologists and obstetricians[3].

Various methods have been used to prevent hypotension like pre-hydration, vasopressor drugs and lower leg compression but even then many parturient become hypotensive after spinal anaesthesia and require treatment[4]. Historically, ephedrine was considered the preferred vasopressor for management of spinal-induced hypotension in healthy parturients. Ephedrine has a relatively slow onset and long duration of action compared to Phenylephrine .Ephedrine is a mixed ± and ² agonist and causes increase in cardiac output and heart rate. Ephedrine crosses placenta and causes increase in oxygen consumption and increase in glucose and lactic acid concentrations[5]. It has been demonstrated that ephedrine crosses the placenta to a greater extent than phenylephrine and stimulation of ²-adrenergic receptors in the foetus results in an increased foetal metabolic rate. Ephedrine-induced foetal tachycardia and acidosis appears to depend on dosage and timing of drug administration prior to delivery[6].

Phenylephrine, a direct ±1-agonist, was avoided due to concerns regarding potential uterine blood flow reduction[7]. Recent literature review showed that ephedrine and phenylephrine are both effective for the management of hypotension with no difference in neonatal Apgar scores and the incidence of foetal acidosis but phenylephrine was associated with higher neonatal umbilical arterial pH values[8].

The present study was designed to assess the effectiveness of ephedrine and phenylephrine in preventing and treating hypotension in spinal anaesthesia for caesarean section and their effect on foetal outcome.

Materials and Methods

This study was conducted in the Department of Anaesthesia, Analgesia and Critical Care of Combined Military Hospital (CMH) Chittagong from October 2015 to June 2015. After a proper approval and a written informed consent, 100 patients of ASA grade-1 undergoing caesarean section under spinal anaesthesia with a normal singleton pregnancy beyond 37 weeks gestation were selected. Patients with pregnancy-induced hypertension, history of diabetes, cardiovascular and cerebrovascular disease, fetal abnormalities, and contraindication to spinal anaesthesia were excluded from the study. Patients were randomly allocated into two groups of 50 each.

Group 1 received prophylactic bolus of ephedrine 10 mg iv at the time of intrathecal block, plus rescue boluses of 5 mg ephedrine, whenever maternal systolic blood pressure was less than 90 mmHg. Group 2 received prophylactic bolus of 100 ¼g iv of phenylephrine at the time of intrathecal block, plus rescue boluses of 50 ¼g phenylephrine, whenever maternal systolic blood pressure was less than 90 mmHg.

On arrival in the operation theatre heart rate, blood pressure (NIBP), respiratory rate and arterial O_2 saturation (SpO_2) were recorded. All patients preloaded with 10 ml/kg of Ringer lactate saline. Each subject also received injection ranitidine 50 mg and injection metoclopramide 10 mg iv as premedication. Patients were placed in lateral or sitting position according to their convenience. Lumbar puncture was performed with 25 gauge Quincke's needle in L3-L4 intervertebral space. Once free flow of cerebrospinal fluid was obtained, 2.5 ml of 0.5% bupivacaine hyperbaric was administered over 10-15 seconds. Time of injection of drug was noted and patient was placed in supine position immediately with a left lateral tilt of 15-20 degrees. Inspired air was supplemented with oxygen at 4 l/min until clamping of umbilical cord. Immediately after induction of spinal anaesthesia, systolic blood pressure, diastolic blood pressure and heart rate were recorded. At the time of intrathecal injection, patients were given either phenylephrine 100 ¼g iv bolus or ephedrine 10 mg iv bolus. Hemodynamic variables like blood pressure and heart rate was recorded every 2 minutes up to delivery of baby and then after every 5 minutes.

Whenever systolic blood pressure decreased to less than 90 mmHg, vasopressor was administered, either 5 mg of ephedrine or 50 ¼g of phenylephrine. On each occasion when maternal heart rate decreased to below 60 beats per minute (bpm), atropine 0.3 mg iv was administered. Neonatal outcome was assessed using Apgar Score at 1 and 5 minutes and neonatal umbilical cord blood pH values. At delivery umbilical cord was clamped and 1 ml of blood sample collected in heparinized syringe for acid base analysis. Umbilical artery pH value < 7.2 indicates asphyxia.

Statistical analysis: Parametric data was expressed as mean ± SD, thereby the inter group comparisons were made by Student's *t*-test. The test was two sided and referred for *P*-value for its significance. *P*-value less than 0.05 ($P < 0.05$) was taken to be statistically significant. The analysis was performed on SS.

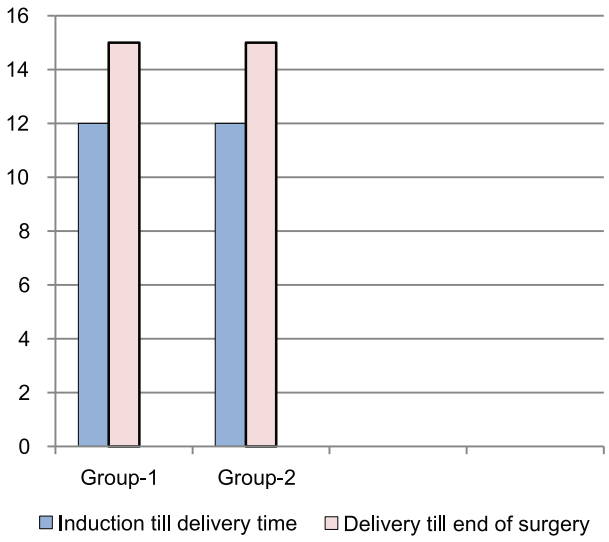

Fig 1 *Comparison between surgical times in groups 1 and 2*

Results

Total 100 patients selected for this study were randomly divided into two groups of 50 patients each. The two groups were matched with regard to their age, body weight (Table-I) and duration of surgery (Figure 1).

The difference observed in baseline heart rate, systolic, diastolic, and mean blood pressures between two groups was statistically insignificant (Table-II). There was higher incidence of bradycardia in patients receiving phenylephrine than those receiving ephedrine. The difference in mean heart rate till delivery compared between two groups and at 2, 4, 6, 8, 10, and 12 minutes was significant while it was insignificant immediately after spinal anaesthesia. (*P*-value < 0.05: significant). The difference in mean heart rate compared between two groups at 5, 10, 20 minutes and at the end of the surgery was insignificant except at delivery and 15 minutes after delivery (*P*-value < 0.05: significant (Table-III) and (Table IV).

Table I *Comparison of age and weight between group 1 and group 2*

Characteristics	Group-1 (n=50) Mean ± SD	Group-2 (n=50) Mean ± SD	*P*-value	Significance
Age (Years)	26.24 ± 0.48	27.23 ± 0.46	0.145	NS
Weight (Kg)	62.48 ± 8.69	65.38 ± 8.12	0.07	NS

NS = Not significant.

Table-II *Comparison of baseline heart rate, systolic, diastolic and mean blood pressure in group 1 and 2*

Characteristics	Group-1 Mean ± SD	Group-2 Mean ± SD	t-value	p-value	Significance
Heart rate	88.30 ± 6.55	86.36 ± 11.02	1.01	0.319	NS
Systolic blood pressure	120.88 ± 11.34	120.96 ± 9.78	0.91	0.923	NS
Diastolic blood pressure	78.30 ± 9.80	76.14 ± 9.28	1.02	0.304	NS
Mean blood pressure	90.20 ± 10.05	92.88 ± 8.75	0.61	0.478	NS

NS = Not significant

Table III *Comparison of heart rate, systolic and diastolic blood pressure between groups 1 and 2 before delivery*

Parameter till	Heart Rate/min			Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)		
delivery	Group-1 Mean ± SD	Group-2 Mean ± SD	*P*-value	Group-1 Mean ± SD	Group-2 Mean ± SD	*P*-value	Group-1 Mean ± SD	Group-2 Mean ± SD	*P*-value
Immediately after SA	90.38±21.43	85.01±12.01	0.070	107.84±14.85	106.301±13.55	0.841	68.66±11.77	67.80±10.49	0.946
2 min after SA	90.7±21.38	82.52±17.84	0.001	117.76±17.42	110.11±17.40	0.061	77.421±11.72	73.031±12.83	0.053
4 min after SA	97.74±19.37	80.88±15.90	0.001	112.19±18.03	106.60±17.94	0.087	73.461±11.14	74.061±10.65	0.760
6 min after SA	91.70±14.07	80.26±16.14	0.003	108.44±20.19	104.96±16.84	0.500	74.80±13.17	76.11±12.54	0.621
8 min after SA	93.20±15.19	83.80±17.31	0.021	110.92±14.29	105.451±14.90	0.077	74.66±11.60	73.19±11.50	0.509
10 min after SA	90.82±15.05	82.24±15.18	0.036	108.82±10.46	104.76±14.56	0.091	76.16±11.17	75.82±9.40	0.524
12 min after SA	92.62±14.83	83.44±15.33	0.055	112.94±12.44	108.54±10.40	0.073	74.51±8.18	76.11±8.29	0.611

Table IV *Comparison of mean pulse rate, systolic blood pressure and diastolic blood pressure between group 1 and 2 after delivery*

Parameter	Heart Rate/min			Systolic Blood Pressure (mmHg)			Diastolic Blood Pressure (mmHg)		
	Group-1 Mean ± SD	Group-2 Mean ± SD	*P*-value	Group-1 Mean ± SD	Group-2 Mean ± SD	*P*-value	Group-1 Mean ± SD	Group-2 Mean ± SD	*P*-value
At delivery	95.30±13.40	86.78±13.00	0.03	102.04±11.22	100.66±12.30	0.21	66.90±11.71	64.72±8.70	0.43
5 min after SA	90.22±14.80	87.10±13.21	0.08	106.12±15.33	108.48±14.04	0.71	70.12±11.21	68.741±10.50	0.73
10 min after SA	88.22±13.16	86.21±12.19	0.43	114.82±17.41	110.52±17.06	0.25	75.86±12.43	72.941±11.27	0.09
15 min after SA	93.52±8.80	84.53±15.16	0.01	116.04±14.53	112.40±14.80	0.56	74.82±8.01	73.16±9.59	0.09
20 min after SA	90.67±5.49	88.84±7.58	0.93	115.01±8.28	104.651±19.62	0.07	70.21±8.14	69.90±10.42	0.41
End of Surgery	90.06±6.92	87.85±12.96	0.21	114.01±13.58	112.72±12.70	0.89	74.04±9.26	72.66±7.76	0.16

The difference in systolic, diastolic, and mean blood pressure between two groups till delivery and after delivery at all times was statistically insignificant. Overall, 35/ 55(52%) patients in the phenylephrine group and 30/50 (50%) patients in ephedrine group had one or more episode of hypotension and required one or more bolus of vasopressor. The number of rescue doses required in group 1 and 2 were statistically insignificant (Table III), (Table IV), (Table V), (Table VI) (*P*-value < 0.05: significant).

Table V *Comparison of mean blood pressure (mmHg) till delivery between group 1 and 2*

Mean BP (mmHg)	Group-1 Mean ± SD	Group-2 Mean ± SD	t-value	*P*-value	Significance
Immediately after SA	82.37 ± 11.64	80.38 ± 9.92	0.035	0.961	NS
2 min after SA	88.11 ± 10.41	87.84 ± 12.91	1.773	0.076	NS
4 min after SA	85.17 ± 12.14	88.32 ± 12.11	0.331	0.761	NS
6 min after SA	86.94 ± 13.70	90.80 ± 13.16	0.382	0.811	NS
8 min after SA	86.12 ± 12.65	86.80 ± 12.90	0.730	0.410	NS
10 min after SA	88.08 ± 11.43	87.14 ± 10.17	0.841	0.362	NS
12 min after SA	87.11 ± 9.11	88.26 ± 9.26	0.743	0.441	NS

NS = Not significant.

Table VI *Comparison of mean blood pressure (mmHg) after delivery in groups 1 and 2*

Mean BP (mmHg)	Group-1 Mean ± SD	Group-2 Mean ± SD	t-value	*P*-value	Significance
At delivery	82.59 ± 11.01	80.92 ± 9.52	0.982	0.323	NS
5 min after delivery	84.68 ± 11.60	86.18 ± 12.71	0.393	0.691	NS
10 min after delivery	88.93 ± 12.35	87.29 ± 12.77	1.721	0.082	NS
15 min after delivery	87.70 ± 9.17	86.78 ± 9.36	1.661	0.102	NS
20 min after delivery	85.12 ± 9.01	87.39 ± 10.75	1.047	0.275	NS
At the end of surgery	88.38 ± 8.94	86.69 ± 7.80	1.060	0.292	NS

NS = Not significant.

The difference in birth weight of neonates between two groups was statistically non-significant (Table VIII). No neonate had Apgar score <7 at 1 or 5 minute. Mean neonatal umbilical cord pH in group 1 was 7.33±0.04 and in group 2 it was 7.36±0.04. Patients given phenylephrine had neonates with higher umbilical cord pH than those given ephedrine but the difference was statistically non-significant (Table-VII).

Table VII *Comparison of birth weight and umbilical cord pH between group 1 and 2*

Parameter	Birth weight (grams)	Umbilical cord pH
Group-1	2851 ± 512.7	7.33 ± 0.04
Group-2	3027 ± 422.82	7.36 ± 0.04
P-value	0.822	0.270

P-value <0.05: Significant

Discussion

Maternal hypotension is the most common and important physiological response to spinal anaesthesia due to preganglionic sympathetic block with important maternal and foetal consequences. In literature overall incidence of hypotension during spinal anaesthesia for caesarean section is 80%[9]. Hypotension remains a common clinical problem after induction of spinal anaesthesia during caesarean delivery. It has been associated with considerable morbidity (maternal nausea and vomiting and foetal/neonatal acidaemia. Traditionally, non-pharmacological interventions such as leg elevation, compressive leg devices, left uterine displacement and intravenous fluid preloading have been used but vasopressors are often required[10].

Because of the poor efficacy of non pharmacological techniques to effectively manage hypotension, a vasopressor is usually required during spinal anaesthesia for caesarean section. In choosing an appropriate vasopressor in obstetrics, a number of factors like efficacy for maintaining blood pressure, non-cardiovascular maternal effects, ease of use, direct and indirect fetal effects, cost, and availability need to be considered[11].

Ephedrine and phenylephrine have been used for the treatment of intra-operative hypotension in many studies. Ephedrine is effective in the treatment of spinal induced hypotension during caesarean sections, but it can cause foetal acidosis[12]. Updated meta-analysis by Lin FQ et al. showed comparable results between prophylactic ephedrine and phenylephrine to manage spinal-induced hypotension but parturient treated with phenylephrine had neonates with higher umbilical pH value than those treated with ephedrine[13].

Ephedrine is a mixed ± and ² agonist and causes increase in cardiac output and heart rate. Ephedrine crosses placenta and causes increase in oxygen consumption and increase in glucose and lactic acid concentrations. Phenylephrine is a pure ±1 adrenergic agonist, which increases systemic vascular resistance and causes reflex bradycardia but it maintain cardiac output in healthy parturient[14].

In this study, all patients in the two groups were comparable with respect to age and ASA status.

The difference observed in baseline parameters, that is, pulse, systolic, diastolic and mean arterial pressures between two groups was statistically insignificant, respectively. There was statistically non-significant difference between surgical times (induction to delivery time and from delivery till end of surgery) in groups 1 and 2.

In this study, there was higher incidence of bradycardia in patients receiving phenylephrine than those receiving ephedrine This is expected to be due to increase in blood pressure with an ±-agonist may lead to reactive bradycardia (baroreceptor reflex). However, this was responsive to atropine without adverse consequences. There was no difference in maximum recorded heart rate between two groups. The results of this study were in accordance with the study of Lee *et al*.[15] in which they reported higher incidence of bradycardia in patients receiving phenylephrine as compared with patients receiving ephedrine for prevention of hypotension during spinal anaesthesia for caesarean section. The results of this study are in accordance with the study of Adigun *et al*.[16] They observed that both vasopressors effectively restored both the systolic and diastolic blood pressure. They also concluded that phenylephrine is safe and can be used as effectively as ephedrine. Their study also compared intravenous ephedrine with phenylephrine for the maintenance of arterial blood pressure during caesarean section under spinal anaesthesia. The mean Apgar scores were similar for the two groups; no baby had Apgar score of <8 in either group. The results are in accordance with this study.

Gunda et al. compared the effectiveness and the side effects of ephedrine and phenylephrine administered for treating hypotension during caesarean section under spinal anaesthesia and found that both are effective in treating hypotension. They suggested that phenylephrine may be more appropriate vasopressor when considering maternal wellbeing[17].

However, this study showed that women who received phenylephrine had neonates with higher umbilical cord pH than women who received ephedrine, although the risk of true foetal acidosis (Umbilical artery pH<7.20) was similar. No neonate in both groups had pH < 7.2. Prakash *et al* [18] found that women who were given phenylephrine had neonates with higher umbilical arterial pH values than those given ephedrine. There was no difference between two groups in the incidence of true foetal acidosis similar to this study finding.

Cooper *et al*. [19] concluded in their study that the umbilical artery pH was similar, whether ephedrine or phenylephrine was used to maintain maternal arterial pressure, which is consistent with this study. Acidotic changes in umbilical artery are sensitive indicators of utero-placental insufficiency. The study finding is indirect evidence that uterine blood flow may in fact be better with phenylephrine compared with ephedrine. The exact reason how ephedrine causes acidosis is unknown. One of the reasons is that it crosses through placenta and has a direct effect on fetus to cause acidosis. There was no difference in Apgar score between the two groups. In this study, no neonate had an Apgar score < 7 at 1 or at 5 minutes. The difference in birth weight of neonates between two groups was statistically non significant. Apgar score is the most commonly applied and easily interpretable clinical method of neonatal wellbeing and in literature. A recent meta-analysis of vasopressor choice during regional anesthesia in obstetric showed phenylephrine and ephedrine are comparable in terms of neonatal Apgar score at one and five minutes after delivery.[20]

Conclusion

We conclude from this study that ephedrine and phenylephrine are equally efficient in managing hypotension during spinal anaesthesia for caesarean section. There was no difference between two vasopressors in the incidence of true fetal acidosis. Neonatal outcome remains equally good in both the groups.

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