

Comparison of Bolus Phenylephrine, Ephedrine and Mephentermine for Maintenance of Arterial Pressure during Spinal Anesthesia in Cesarean Section

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ABSTRACT

Introduction: Hypotension is common following spinal anesthesia. Various vasopressors have been indicated to prevent it. The study compares three such agents namely phenylephrine, ephedrine and mephentermine.

Methods: The study included 90 patients undergoing elective and emergency cesarean section who developed hypotension following subarachnoid blockade. Parturient were randomly divided into three groups each group had 30 patients. Group P received bolus of Phenylephrine 25 microgram, where as group E received Ephedrine 5mg and Group M received Mephentermine 6mg.

Results: It was found that rise of blood pressure was significantly higher in case of phenylephrine group in first six minutes, after the bolus, there was significant reduction in the heart rate in phenylephrine group, but there was tachycardia following administration of bolus ephedrine and mephenteramine. Neonatal APGAR score were similar in all three groups.

Conclusions: All three drugs maintained hemodynamics within 20 percent of the baseline values on intravenous administration.

Key Words: APGAR, ephedrine, hypotension, mephentermine, phenylephrine, spinal anesthesia

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INTRODUCTION

Hypotension is common following spinal anesthesia with the incidence up to 80% despite fluid preload and lateral uterine displacement.¹ During cesarean section done under spinal anesthesia, maternal hypotension is associated with dizziness, nausea, vomiting, and can also cause fetal bradycardia² and acidosis.³ Management of hypotension includes administration of fluids, and preemptive administration of vasopressors. In 1965, Gries and Crandell showed rapid infusion of crystalloid helped partially restore uterine blood flow.⁴ But crystalloids have short half life and over infusion can cause dilutional anemia.⁵ Thus the patient may be at greater risk of pulmonary edema.⁶

Several other methods have been tried to prevent hypotension like left uterine displacement⁷, leg compression and elevation⁸, prophylactic administration of phenylephrine and ephedrine⁹, angiotensin II¹⁰ and atrial natriuretic peptide.¹¹

This study evaluates the effects of intravenous phenylephrine 25 micrograms, ephedrine 5 milligram and mephentermine 6 milligram as a vasopressor therapy in case of hypotension associated with spinal anesthesia in patients undergoing cesarean section.

METHODS

This is a prospective, interventional study conducted among 90 parturients undergoing elective or emergency caesarian sections at Lady Goshen Hospital, Mangalore from May 2007 to May 2008. Only those who consented to the study were included.

Patients with hypertensive disorders of pregnancy, (defined as systolic blood pressure of more than 140 mm of Hg and diastolic pressure of more than 100mm of Hg), polyhydramnios, multiple pregnancies, suspected intrauterine growth retardation, hemoglobin of less than 9 gram per deciliter and the patients with co existing medical diseases were excluded from the study.

After pre anesthetic examination, the elective cases were premedicated with ranitidine 150 mg at night and metoclopramide 10mg and ranitidine 50 mg intravenous one hour before surgery. Emergency cases were premedicated with intravenous 50 mg of ranitidine and 10mg of metoclopramide at the time of pre anesthetic examination. Patients were preloaded with Ringer lactate 10ml/kg via 18G cannula.

Patients were shifted to operating suit in left lateral position and oxygen was started with Hudson's mask at rate of 6 liters per minute irrespective of oxygen saturation. Oxygen was continued till the baby was extracted and umbilical cord clamped.

Blood pressure was taken thrice before and after preloading, and the mean values were taken as the baseline. Then with all aseptic precautions 2ml of 0.5% hyperbaric bupivacaine was instilled in the sub arachnoid space in L₃- L₄ interspace using 23G spinal needle after confirming free flow of cerebro spinal fluid. The patient was turned supine immediately and wedge was kept under the right flank. This was considered as time zero. Blood pressure measurement was done at time zero. Immediately after, blood pressure of the patient was taken every three minutes for first half an hour then every five minutes till the end of surgery. Injection Oxytocin 20 units in Ringer lactate as slow intravenous infusion was started after cord was clamped.

The patients were randomly grouped into group P, group E and group M. Group P received phenylephrine 25 microgram, Group E received ephedrine 5mg as bolus and Group M received mephentermine, 6 mg as bolus, if there was hypotension, which was defined as fall in Blood pressure of 20% of baseline or systolic blood pressure of >90mmhg. Complications like bradycardia, (defined as heart rate of less than 60) nausea and vomiting were treated accordingly. APGAR score of the child was taken by the pediatrician who was blinded to the vasopressor used.

Block height in each group time, onset of block and time of onset of hypotension and number of boluses required were noted. The results were analyzed statistically using SPSS V 16. Intergroup comparison was done by one way Analysis of Variance (ANOVA). A p value of less than 0.05 was considered to be statistically significant. The study was ethically approved by the hospital ethical board.

RESULTS

All the three groups were comparable in demographic profiles and baseline parameters. Maternal heart rate, maternal systolic Blood Pressure, maternal diastolic blood pressure, hemoglobin and fetal heart rate was similar in all three groups. Three groups were comparable in subarachnoid block to hypotension time, subarachnoid block to delivery time and APGAR at 1 and 6 minutes (Table 1).

Table 1. Comparison of demographic profiles in three group of patients

Parameters	Group P	Group E	Group M	p-value
Age (years)	25.23 ± 3.21	24.89 ± 3.54	24.58 ± 3.39	0.740
Weight (kg)	55.40 ± 5.55	55.20 ± 5.33	54.83 ± 6.25	0.999
Height (cm)	148.16 ± 4.25	148.75 ± 4.42	149.09 ± 3.99	0.993
Parity	1.60 ± .72	1.68 ± 0.71	1.58 ± 0.764	0.793
Maternal heart rate (bpm)	89.27 ± 10.6	89.03 ± 10.42	90.84 ± 9.52	0.652
Maternal SBP (mm Hg)	116.53 ± 5.40	116.90 ± 6.60	114.16 ± 19.57	0.652
Maternal DBP (mm Hg)	76.17 ± 4.676	76.38 ± 5.328	75.97 ± 4.902	0.950
Fetal heart rate (bpm)	141.73 ± 4.835	141.41 ± 5.039	140.03 ± 6.7	0.456
SAB to hypotension	3.63 ± 3.33	4.55 ± 0.42	4.20 ± 2.71	0.941
SAB to delivery	12.06 ± 4.68	12 ± 4.55	10.54 ± 10.87	0.947
APGAR at 1 min	7.40 ± 0.814	7.31 ± 0.806	7.32 ± 0.791	0.897
APGAR at 6 min	9.00 ± 0.000	9.00 ± 0.000	9.00 ± 0.000	NS

There was statistically significant decrease in the blood pressure at the onset of hypotension. There was significant rise in the blood pressure after administration of the drug. On intergroup comparison, systolic blood pressure in phenylephrine group was higher than in other groups. The rise in blood pressure post drug administration was significantly higher in phenylephrine group as compared to mephentermine group (Table 2).

Table 2. Changes in systolic blood pressure

Time Interval	Systolic Blood Pressure			Intergroup Comparison		
	Group P	Group E	Group M	P-M	P-E	E-M
SBP _{Pre op}	116.17 ± 4.67	118.38 ± 5.32	115.97 ± 4.90	-	-	-
SBP ₀	120.00 ± 8.30	120.69 ± 7.87	120.00 ± 7.85	-	-	-
SBP ₃	104.33 ± 7.16	102.07 ± 7.73	101.61 ± 7.89	-	-	-
SBP ₆	110.33 ± 12.17	103.03 ± 7.36	105.81 ± 8.47	++	++	-
SBP ₉	116.83 ± 6.36	108.28 ± 5.86	109.13 ± 9.49	++	++	-
SBP ₁₂	117.67 ± 5.83	109.83 ± 5.08	109.84 ± 7.12	++	++	-
SBP ₁₅	116.83 ± 4.82	111.72 ± 9.28	112.26 ± 7.51	-	-	-
SBP ₁₈	114.17 ± 6.95	108.62 ± 8.54	109.84 ± 9.87	++	++	-
SBP ₂₁	113.33 ± 6.34	107.76 ± 7.97	110.81 ± 7.53	-	-	-
SBP ₂₄	115.33 ± 8.29	110.00 ± 6.68	110.97 ± 8.40	++	++	-
SBP ₂₇	112.33 ± 8.97	109.83 ± 7.25	111.77 ± 11.22	-	-	-
SBP ₃₀	115.83 ± 8.31	110.34 ± 7.55	113.39 ± 7.89	-	-	-

Within the Groups P < 0.001, P < 0.05, ° P > 0.05. Between the Groups + P < 0.001, ++ P < 0.05, - P > 0.05.

There was also significant rise of diastolic blood pressure post administration of the drug but rise was more in phenylephrine group than in ephedrine and mephentermine group. There was no significant difference in the change in the blood pressure in between ephedrine and mephentermine group (Table 3).

Table 3. Changes in diastolic blood pressure

Time Interval	Systolic Blood Pressure			Intergroup Comparison		
	Group P	Group E	Group M	P-M	P-E	E-M
DBP _{Pre op}	76.17 ± 4.67	76.38 ± 5.32	75.97 ± 4.90	-	-	-
DBP ₀	77.17 ± 5.97	77.24 ± 5.27	76.61 ± 5.06	-	-	-
DBP ₃	65.50 ± 5.30	65.86 ± 5.01	64.84 ± 5.08	-	-	-
DBP ₆	71.83 ± 7.13	64.48 ± 4.29	66.77 ± 5.56	++	++	-
DBP ₉	77.83 ± 3.13	71.03 ± 4.09	76.45 ± 2.94	-	-	-
DBP ₁₂	78.83 ± 2.52	73.45 ± 5.01	77.42 ± 3.62	-	++	-
DBP ₁₅	74.50 ± 4.22	71.38 ± 6.53	71.94 ± 4.774	-	-	-
DBP ₁₈	73.67 ± 6.00	68.62 ± 6.25	71.13 ± 5.58	-	-	-
DBP ₂₁	72.33 ± 5.04	67.93 ± 4.33	69.35 ± 4.23	-	-	-
DBP ₂₄	73.67 ± 6.42	69.14 ± 4.02	72.10 ± 7.50	++	++	++
DBP ₂₇	72.83 ± 7.62	71.03 ± 5.06	72.58 ± 6.56	-	-	-
DBP ₃₀	74.00 ± 5.15	70.34 ± 5.49	73.55 ± 6.35	-	-	-

Within the Groups P < 0.001, P < 0.05, ° P > 0.05. Between the Groups +P < 0.001, ++ P < 0.05, - P > 0.05.

Heart rate was raised in all three groups during hypotension, which was significant, but post drug administration there was significant drop in the heart rate in phenylephrine group as compared to Ephedrine and Mephentermine group. Where as in group E and M there was rise in heart rate post administration of the drug (Table 4).

Table 4. Changes in heart rate

Time Interval	Systolic Blood Pressure			Intergroup Comparison		
	Group P	Group E	Group M	P-M	P-E	E-M
HR Pre op	83.63 ± 7.04	86.34 ± 7.33	86.94 ± 6.39	-	-	-
HR ₀	83.63 ± 7.03	86.34 ± 7.33	86.94 ± 6.39	-	-	-
HR ₃	93.83 ± 4.86	91.66 ± 6.40	93.61 ± 4.87	-	-	-
HR ₆	81.67 ± 9.93	93.38 ± 6.43	91.19 ± 8.83	++	++	-
HR ₉	82.30 ± 5.55	91.97 ± 5.55	90.32 ± 5.00	++	++	-
HR ₁₂	84.20 ± 5.73	93.21 ± 5.88	95.23 ± 4.46	++	++	-
HR ₁₅	84.13 ± 4.87	90.86 ± 5.38	90.00 ± 3.26	++	++	-
HR ₁₈	85.70 ± 5.51	90.41 ± 3.97	90.77 ± 2.40	++	++	-
HR ₂₁	85.87 ± 6.68	90.83 ± 5.76	90.90 ± 5.96	++	++	-
HR ₂₄	85.37 ± 5.04	91.90 ± 4.55	91.87 ± 5.90	++	++	-
HR ₂₇	87.43 ± 8.23	92.31 ± 5.4	94.68 ± 6.72	++	++	-
HR ₃₀	83.50 ± 6.45	91.00 ± 4.8	89.00 ± 2.29	++	++	-

The number of bolus required in Phenylephrine was significantly higher whereas Ephedrine and mephentermine group required similar number of boluses (Table 5).

One patient in group P complained of nausea and three patients in ephedrine complained of thumping heart. There was no significant difference in APGAR score, all three group had APGAR of more than 7.

Table 5. Number of boluses required in each group

Group	Mean number of bolus	Standard deviation
P	3.51	0.51
E	2.54	0.52
M	2.87	0.37

DISCUSSION

One of the commonest complications of spinal anesthesia is hypotension.¹ Undertreated and over treated hypotension occurring during cesarean section delivery can cause undue effects to both mother and fetus.² There have been several attempts to find the optimal therapy for hypotension occurring during cesarean section. Several measures to prevent hypotension include left uterine displacement⁷, application of tight fitting stockings⁸, preloading with colloids and crystalloids¹² and prophylactic intramuscular administration of vassopressor agents.^{9,13} All these maneuvers have their own limitations. Fluid preloading, although considered to be standard practice, has been shown to be non effective. Tight fitting elastic stockings, although help in some degree, their use is limited by the cost and moreover over they are not stand alone method to prevent hypotension.⁸ Intramuscular administration of vassopressors has been found to cause hypertension and fetal acidosis⁹, so this practice has been abandoned. So the use of vassopressor during the time of hypotension is appropriate, as arterial vasodilatation is the main cause of hypotension. It has been shown that the percentage decrease in placental circulation is related to percentage reduction in maternal arterial pressure but not absolute reduction in pressure. So administration of vasopressor agent whenever it's appropriate is logically correct. Hypotension in most of the studies has been defined as values ranging from 20 to 30 percent reduction from baseline systolic arterial pressure or mean arterial pressure. Incidence of hypotension clearly depends on the definition. For the purpose of our study we defined hypotension as reduction in arterial pressure by 20% from the baseline systolic pressure.

Phenylephrine is directly acting alpha 1 adrenergic agonist where as Ephedrine and Mephentermine act indirectly on both alpha and beta receptors. Although phenylephrine

has only alpha adrenergic activity, earlier it was considered to cause reduction in uterine blood flow, but Naag et al¹⁴ in his review mentioned that phenylephrine causes less fetal acidosis than ephedrine. Other studies using phenylephrine in pregnant patients have also found that although it causes fetal acidosis, it's less than that caused by ephedrine and is non detrimental to neonatal outcome.¹⁵⁻²⁰

Thomas and colleagues¹⁵ reported that bolus phenylephrine 100 microgram is as effective as ephedrine 5 mg in restoring maternal blood pressure above 100 mm of Hg. Moron and colleagues¹⁶ gave ephedrine 10 mg or phenylephrine 80 microgram bolus to maintain systolic blood pressure above 100. Ramanathan and colleagues¹⁷ studied 127 healthy patients undergoing cesarean section under epidural anesthesia and they concluded that transient maternal hypotension does not affect the neonatal acid base status.

In our study all the three vasopressor agents maintained Blood pressure within 20% of baseline values, though phenylephrine maintained better in first six minutes. This can be attributed to the peak onset of phenylephrine within one minute, but this group required more number of bolus, which can be attributed to short duration of action of intravenous bolus (about 10 minutes). Where as in other groups, peak onset was slightly slow which can be attributed to onset of action of ephedrine 2-5 and mephentermine in five minutes.

In our study phenylephrine causes significant reduction in heart rate after the bolus dose, which is a consistent effect in phenylephrine treated women in other studies. In spinal anesthesia, since there is decreased venous return, decreased venous pressure and a decreased right heart pressure thus slowing of the heart rate is expected on the basis of the Bainbridge reflex. Bradycardia is also expected in high spinal, probably due to some paralysis of the cardiac accelerator nerve. We found that the maternal heart rate was slower with phenylephrine than with ephedrine and mephentermine. This can be attributed to selective action on alpha receptors and no action on beta receptors. Studies by Thomas DG et al showed significant bradycardia that warranted treatment. Our study had none as the bolus drug was 25 microgram in our case whereas it was 100 microgram in that study.

CONCLUSIONS

The study found that all three drugs maintained hemodynamic within 20 percent of the baseline values on intravenous administration. There was no undue effect on the mother and the fetus as assessed by hemodynamic parameter and fetal APGAR scores.

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