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Prophylactic administration of two different bolus doses of phenylephrine for Prevention of spinal -induced hypotension during cesarean section: A Prospective double-blinded Clinical Study

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KEYWORDS
Oral prophylactic administration, phenylephrine, spinal-induced hypotension, cesarean section

ABSTRACT

Aim: The aim of the present study was Prophylactic administration of two different bolus doses of phenylephrine for Prevention of spinal - induced hypotension during cesarean section: A Prospective double-blinded Clinical Study

Methods: This prospective double-blinded study was conducted at Department of Anaesthesiology and CCM, IGIMS, Patna, Bihar, India for the period of one year. We enrolled 150 parturients of American Society of Anesthesiologists (ASA) grade I or II between 18 to 35 years of age and posted for elective cesarean delivery under spinal anesthesia.

Results: Demographic and obstetric data such as age, weight of mother, gestation week, parity, and duration of surgery and anesthesia were comparable in all the three groups. The total fluid requirement of the control group was significantly more ($P < 0.001$) as compared to the other two groups. Incidence of hypotension was significantly ($P < 0.001$) more in the control group (72%) than groups P75 (24%) and P100 (18%). The need for administering rescue vasopressors was significantly delayed in groups P75 and P100 ascompared to the control group. The total dose volume (mg) and the number of doses of phenylephrine were significantly higher in the control group than in the groups P75 and P100 ($P < 0.001$).The P100 group showed a significant fall in HR from baseline after 4 min of SAB and remained significantly low throughout the intraoperative period ($p < 0.001$). The mean value of lowest HR (bpm) was highly significant in P100 as compared to P75 and P0. Higher incidence of bradycardia was observed in group P100 (38%) than P75 (16%) and control group (10%).

Conclusion: Prophylactic administration of bolus phenylephrine significantly decreases the incidence of maternal hypotension and a dose of 75 µg is adequate to prevent post-spinal hypotension for cesarean delivery without any detrimental effect on the neonatal and maternal outcomes.

INTRODUCTION

Spinal anesthesia is the preferred technique for an elective cesarean section as it avoids airway manipulation and the complications of general anesthesia.[1] However, if not actively prevented by pharmacological measures, it causes maternal hypotension in most women, with the incidence being as high as 60%.[2,3] The use of vasopressors is the most reliable method of counteracting hypotension and is highly recommended as prolonged maternal hypotension can lead to serious side effects such as nausea, vomiting, cardiovascular instability, decreased blood flow to the uteroplacental complex, and consequent fetal acidosis.[4]

The most commonly used vasopressors are phenylephrine and ephedrine. Ephedrine is associated with maternal tachycardia and decreased fetal pH.[5] Phenylephrine has been reported to be accompanied by a dose-related decrease in maternal heart rate (HR) and the subsequent fall in cardiac output.[6] Recently,

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norepinephrine has been proposed as an alternative vasopressor in obstetric anesthesia owing to its dual α- and β-agonist activity.[7,8]Prophylactic infusion of vasopressors with a rescue bolus dosing was observed to be more effective for hemodynamic stability when compared to administering a bolus dose alone. The advantages included reducing the workload of clinicians while providing increased maternal comfort.[9]

Hypotension can have detrimental effects on neonate, which include decrease in uteroplacental flow, impaired fetal oxygenation with asphyxia and fetal acidosis.[10] Preventive measures for hypotension include adequate preload (10–15 mL/kg), lateral tilt, wedge and use of vasopressors.[11] Ephedrine is the preferred vasopressor in cesarean sections. It has both direct and indirect mechanism of action, stimulating mainly beta receptors (β1 and β2), causing increased cardiac output, heart rate (HR) and systolic blood pressure (SBP) and diastolic blood pressure (DBP). But it can cause supraventricular tachycardia, tachyphylaxis and fetal acidosis.[12]Phenylephrine, a selective α1 adrenergic agonist, is as effective as ephedrine in the treatment of spinal hypotension with a better neonatal outcome and fetal acid–base status.[13] It elevates the blood pressure without increasing the HR or contractility.

The aim of the present study was to compare the effects of prophylactic administration of two different doses of phenylephrine on the incidence of spinal-induced hypotension during cesarean section.

MATERIALS AND METHODS

This prospective double-blinded study was conducted at Department of Anaesthesiology and CCM, IGIMS, Patna, Bihar, India for the period of one year. We enrolled 150 parturients of American Society of Anesthesiologists (ASA) grade I or II between 18 to 35 years of age and posted for elective cesarean delivery under spinal anesthesia. Parturients with complications like risk of excessive bleeding (placenta previa, prolonged labor, abnormal presentation, multiple gestation) pre-existing or pregnancy-induced hypertension, cardiovascular disease, cerebrovascular disease, severe anemia, diabetes, multiple gestation, known fetal abnormality, contraindication for spinal anesthesia, known allergy to phenylephrine, maternal systolic blood pressure (SBP) <100 mm Hg, and inability or refusal to give informed consent were excluded from the study. The study was approved by the Institutional Research Ethics Board and informed consent was obtained from all the patients.

Parturients were randomly divided in to three groups, group P0 (control group),group P75 (phenylephrine 75 mcg), group P100(phenylepherine 100mcg).Group assignments were sealed with in opaque envelopes and were opened by the principal anesthesiologist just before the administration of subarachnoid block (SAB) to the patient. Another anesthesiologist who was not involved in the study prepared the phenylephrine dose according to the randomization group. Parturients and principal anesthesiologists who monitored and recorded the hemodynamic parameters were blinded to the group assignment.

Following preanesthetic evaluation, all the parturients received oral ranitidine (150 mg) the night before and the morning of the day of surgery with a sip of water. Then, through an 18-gauge cannula, lactated Ringer's solution was infused at the rate of 10 ml/kg/hour in the preoperative room and IV injection of ondansetron 4 mg were administered as premedications. The SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and HR were measured at 1-minute intervals using an automated noninvasive monitor in both supine and standing positions. A total of six recordings were taken (three in supine and three in standing) and an average of the three readings in each position was taken preoperatively to test the orthostatic cardiovascular reflexes with change in position. Any parturient developing <20% baseline SBP were infused with crystalloids at 15 ml/kg/hr. Once the parturient was hemodynamically stable, she was shifted into the operation theatre.

In the operating room, standard monitoring included pulse oximetry, electrocardiogram, and noninvasive blood pressure. The patient was placed in the left lateral position, skin was decontaminated with povidione iodine, and a standard dose of 12.5 mg of 0.5% bupivacaine heavy was administered in the subarachnoid space (L3-L4 or L2-L3) using a 25-gauge Quincke needle. Another anesthesiologist blinded to the group allocation, administered the study drug intravenously immediately after the spinal injection at time 0.

Hypotension (fall in SBP to less than 20% of baseline) was treated with maximum two doses of phenylephrine (100 µg) and, if hypotension persisted or bradycardia occurred, another rescue vasopressor (ephedrine 6 mg IV bolus) was administered. Bradycardia (HR less than 55 beats per minute) was treated with an IV bolus of atropine sulfate (0.6 mg). Demographic and obstetric data like age, weight, parity, gestation week, total fluids,

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www.jchr.org
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and duration of surgery and anesthesia were noted in a structured proforma. Block height was assessed bilaterally by using pin prick technique at 5-min intervals for the first 15 min following spinal anesthesia. Surgery was allowed if block height reached the T6 dermatome. If the block height failed to reach the dermatome, then IV analgesics (fentanyl 25 mcg, ketamine 20 mg) were given and the patients were withdrawn from the study. Hemodynamic data (HR, SBP, DBP, and MAP) were recorded from the time of spinal injection and subsequently at every 2-min interval for 10 min and then every 5 min upto 30 min or till the end of surgery. The time of first rescue vasopressor, total number of doses required, and the total dose of vasopressors used to treat the first hypotensive episode along with dose of rescue vasopressor (ephedrine) required were noted. The number of patients developing bradycardia (<55 bpm) were noted and treated with IV atropine 0.6 mg. Adverse effects like nausea, vomiting, shortness of breath, and chest pain were recorded. In addition, the total duration of surgery and anesthesia, total fluid required during surgery along with APGAR score at 1 min and 5 min, requirement of neonatal intensive care, and the weight of baby were also recorded.

Statistical analysis

Statistical analysis was done using SPSS (version 16) software. Analysis of variance (ANOVA) was used to find the significance between the three groups for continuous variables and paired t-test was used for intragroup comparison. Chi-square test was used to find the significance of study parameters on a categorical scale. Results were expressed as mean ± standard deviation and $P < 0.05$ was considered statistically significant.

RESULTS

Table 1: Demographic and Obstetric data

Parameters	**Control Group(*n*=50)**	**P_{75}Group (*n*=50)**	**P_{100}Group (*n*=50)**	**p-value**
Age (yrs)	26.16±4.52	26.54±2.88	27.43±2.38	0.22
Weight(Mother)Kg	65.62±3.72	66.24±4.86	67.53±4.60	0.19
Gestation week	38.57±0.70	38.53±0.75	38.51±0.80	0.80
Parity	1.52±0.54	1.56±0.54	1.76±0.64	0.17
DurationofSurgery (minutes)	30.76±5.12	33.77±5.45	34.00±5.35	0.58
TotalFluids(ml)	1355.0±202.3	1202.0±162.74	1172.0±182.8	<0.001

Demographic and obstetric data such as age, weight of mother, gestation week, parity, and duration of surgery and anesthesia were comparable in all the three groups. The total fluid requirement of the control group was significantly more ($P < 0.001$) as compared to the other two groups.

Table 2: Requirement of Phenylephrine in different groups

	Control Group(*n*=50)	**P_{75}Group (*n*=50)**	**P_{100}Group (*n*=50)**	***P-value***
Patientswithhypotension	36(72%)	12(24%)	9(18%)	<0.001
Totalrescuedose(mcg)	132±68.72	31±57.33	18.52±36.44	<0.001
Totalnumber.ofdose(*n*)	1.64±0.76	0.32±0.58	0.16±0.34	<0.001
Timetofirstrescuedose(minutes)	7.43±3.57	9.71±4.56	12.72±4.48	<0.001

Incidence of hypotension was significantly ($P < 0.001$) more in the control group (72%) than groups P75 (24%) and P100 (18%). The need for administering rescue vasopressors was significantly delayed in groups P75 and P100 ascompared to the control group. The total dose volume (mg) and the number of doses of phenylephrine were significantly higher in the control group than in the groups P75 and P100 ($P < 0.001$).

Table 3: Intraoperative hemodynamic data

	Control Group(*n*=50)		**P_{75}Group (*n*=50)**		**P_{100}Group (*n*=50)**	
	Minimum	**Maximum**	**Minimum**	**Maximum**	**Minimum**	**Maximum**

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HR (bpm)	78.62±8.12	81.16±6.04	69.31±7.83	78.12±5.25	59.71±4.96	78.12±5.25
SBP(mmHg)	112.68±9.41	125.95±6.64	123.97±8.16	128.72±10.50	123.97±7.19	136.14±8.16
DBP(mmHg)	68.92±9.07	78.92±5.85	76.64±8.32	78.00±5.15	78.42±6.56	78.82±5.17
MAP(mmHg)	83.87±9.44	92.44±4.66	90.55±5.08	95.25±5.48	94.96±3.97	99.27±4.86

The P100 group showed a significant fall in HR from baseline after 4 min of SAB and remained significantly low throughout the intraoperative period ($p < 0.001$). The mean value of lowest HR (bpm) was highly significant in P100 as compared to P75 and P0.

Table 4: Requirement of atropine in different groups

	ControlGroup(*n*=50)	**P_{75}Group(*n*=50)**	**P_{100}Group(*n*=50)**	***P-value***
Patientswithbradycardia	6(12%)	8(16%)	19(38%)	0.05
Totalrescuedose (mg)	0.07±0.16	0.12±0.22	0.25±0.35	<0.001
Totalnumberofdoses	0.12±0.32	0.19±0.37	0.42±0.52	<0.01

Higher incidence of bradycardia was observed in group P100 (38%) than P75 (16%) and control group (10%).

DISCUSSION

Spinal-induced hypotension caused by sympathetic neuronal block during cesarean delivery remains a significant clinical challenge.[14] Maternal symptoms like nausea, vomiting, dyspnea, and adverse fetal effects including depressed APGAR scores have been correlated with the severity and duration of hypotension. According to the international consensus statement on the management of hypotension with vasopressors, the aim should be to maintain the baseline systolic arterial pressure (SAP) at ≥90% before spinal anesthesia and avoid a baseline decrease of <80%.[15] Although, in addition to nonpharmacological methods, prophylactic use of vasopressors has been recommended to prevent or treat spinal-induced hypotension, consensus on the ideal vasopressor is still debated.

Phenylephrine bolus doses were found to be the most appropriate method of intervention to restore systemic vascular resistance and cardiac output. As the HR is a surrogate marker for cardiac output, it has been used as a predictor of spinal hypotension.[16] This is even more pertinent in the poor resource setting, where targeting simple surrogate outcomes such as HR could be explored for practical implementation in clinical guidelines.[17]Various studies have been carried out to evaluate the optimum doses of phenylephrine (20 µg to 100 µg). While a dose of 20 µg has been found to be ineffective, doses as high as 100 µg were found to cause reflex maternal bradycardia. Demographic and obstetric data such as age, weight of mother, gestation week, parity, and duration of surgery and anesthesia were comparable in all the three groups. The total fluid requirement of the control group was significantly more ($P < 0.001$) as compared to the other two groups. Incidence of hypotension was significantly ($P < 0.001$) more in the control group (72%) than groups P75 (24%) and P100 (18%). The need for administering rescue vasopressors was significantly delayed in groups P75 and P100 ascompared to the control group. The total dose volume (mg) and the number of doses of phenylephrine were significantly higher in the control group than in the groups P75 and P100 ($P < 0.001$).Similarly, Lee HM et al[18] also observed slightly more requirement of fluids in the control group (900 ml) than the study group (800 ml; phenylephrine 1.5 mg/kg prophylactically). Although it had no statistical significance, it can be attributed to the increased incidence of hypotension incontrol group (71.7%) which increased the volume of total fluids infused as compared to the study group (37%).

The P100 group showed a significant fall in HR from baseline after 4 min of SAB and remained significantly low throughout the intraoperative period ($p < 0.001$). The mean value of lowest HR (bpm) was highly significant in P100 as compared to P75 and P0. Higher incidence of bradycardia was observed in group P100 (38%) than P75 (16%) and control group (10%).Similarly, a significant concentration-dependent reduction in HR (linear trend; $P < 0.007$) has been observed by Stewert et al.[19] In a systematic review of randomized controlled trials, Lee HM et al[18] concluded that the women receiving phenylephrine were more likely to develop bradycardia (<50 bpm) as compared to those treated with ephedrine. Sayyid et al[20] (2014) and Lee HM et al[18] reported that the incidence of hypotension was significant in the groups that did not receive any prophylactic phenylephrine. Incidence of increase in blood pressure was observed.

Journal of Chemical Health Risks
www.jchr.org
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CONCLUSION

Prophylactic administration of bolus phenylephrine significantly decreases the incidence of maternal hypotension and a dose of 75 µg is adequate to prevent post-spinal hypotension for cesarean delivery without any detrimental effect on the neonatal and maternal outcomes.

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