



## Original Research Article

## Efficacy and safety of intravenous phenylephrine and mephentermine for management of hypotension during spinal anaesthesia: A single blind prospective and comparative study among patients undergoing cesarean section

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## ABSTRACT

**Introduction:** Hypotension is a common side effect when neuraxial analgesia is administered to the obstetric population. To find out the efficacy of mephentermine and phenylephrine for management of hypotension following spinal anesthesia in cesarean section. The study has been undertaken at the Department of Anesthesiology of ESI- PGIMSR, Manicktala, Kolkata, after obtaining approval from Institute Ethical Committee

**Study Design:** Uni-centric randomized, single blind, prospective & comparative study

**Statistical Analysis Used:** Unpaired Student's t-test, chi-square test, Fisher's exact test

**Materials and Methods:** The 40-female scheduled for elective caesarean section were randomly divided into two groups of 20 each. Subarachnoid block was performed with 2.2mL of 0.5% hyperbaric bupivacaine. Prophylactic infusion of vasopressor started at a rate of 60 ml/h of 50 mcg/min for phenylephrine (group P, n=20) and 600 mcg/min for mephentermine (Group M, n=20) Hemodynamic parameters were monitored. At the end of surgery and the patients were transferred to the postoperative care unit (PACU).

**Results:** Considering absolute values of hypotension, both groups are comparable in terms of preventing hypotension; however, phenylephrine had better control of maintenance over blood pressure than that of mephentermine. Reactive hypertension is common in phenylephrine infusion. Bradycardia is more prevalent in phenylephrine infusion than that of mephentermine while tachycardia is more common in mephentermine. Side effects like dyspnea, nausea/vomiting, headache is more common during hypotensive episodes. None of the drugs causes any untoward effect on fetus.

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### 1. Introduction

Advantages of using Subarachnoid block (spinal anesthesia) include the technique's simplicity, its action's rapid initiation, the use of minimum drug volume and concentration, while having suitable muscular relaxation during surgery. Hypotension is a common side effect when neuraxial analgesia/anesthesia is administered to the obstetric population. The hypotensive effects of neuraxial anesthesia are compounded by the physiologic changes of pregnancy and may result in a variety of unpleasant

symptoms for the mother, such as nausea, vomiting, dizziness, and, if sustained, can negatively impact the fetus. Commonly used methods to prevent or treat such hypotension include preloading with fluids, avoidance of aortocaval compression and the administration of vasopressor drugs. Mephentermine is readily available and is the most commonly used vasopressor in India to treat spinal anesthesia induced hypotension, but not many workers have studied and compared it with other vasopressors regarding its safety and efficacy.<sup>1</sup> The English literature mentions only one study in pregnant women that compares mephentermine with ephedrine for the management of spinal anesthesia induced hypotension in obstetric patients.

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Phenylephrine Over last two decades there are consistent evidences from well-designed, randomized, blinded studies in Europe<sup>2,3</sup> the United States<sup>4</sup> and Asia<sup>5</sup> supporting the proposition that phenylephrine is at least as safe and effective and probably preferable to traditionally used drug ephedrine for the treatment or prevention of hypotension at Cesarean section. Decades with having little knowledge and understanding regarding its safety and efficacy. So mephentermine needs further studies. Hence this study was done to compare the safety and efficacy of Mephentermine and Phenylephrine in prevention of hypotension during spinal anesthesia at Cesarean section.

## 2. Materials and Methods

The current study has been planned in accordance with the principles of Helsinki declaration. The study has been undertaken at the Department of Anesthesiology of ESI- PGIMSR, Manicktala, Kolkata, after obtaining approval from Institute Ethical Committee. Study area Operation theatres, ESI-PGIMSR and Hospitals, Maniktala, Kolkata. Study population ASA 1 or 2 women with term, uncomplicated, singleton pregnancy scheduled to undergo elective caesarean section.

### 2.1. Study design

Randomized, single blind, prospective & comparative study.

We have optimized a sample size of 40(20 in each group) after considering  $\alpha$ -error of 0.05,  $\beta$ -error of 0.9.

The patients were randomly divided into two groups of 20 each, using a sealed envelope technique to determine the drug that were used for prevention of hypotension. Patients in the 'phenylephrine group'(P) had received an infusion of phenylephrine hydrochloride, whereas patients in the 'mephentermine group' (M) had received an infusion of mephentermine sulphate. Inclusion criteria ASA 1 or 2 women with term, uncomplicated, singleton pregnancy scheduled to undergo elective caesarean section. Exclusion criteria, Known allergic to study drugs, Contraindications to spinal anesthesia, Any prerenal or renal condition, such as diabetes, pre-eclampsia or chronic hypertension, Patients with placental complications such as placenta previa or abruptio placentae, and cord complications, Any associated congenital anomalies, Patients with baseline SBP < 100 mmHg, Patients with baby birth weight < 2.5kg, Preterm deliveries, Patients suffering from any neurological, psychological, cardiovascular, respiratory, renal, hepatic, metabolic and hematological diseases. WE have study Age, Body weight, height, Hypotension (SBP fall  $\leq$  20% of baseline or absolute value of SBP < 100mmHg whichever is first) Hypertension (>20% of SBP above base baseline) Bradycardia (<60 beats/min), Dyspnea, nausea and vomiting. All the patients were evaluated during preanesthetic outpatient visits and ASA classified.

An informed consent was taken in her own language. They were asked to fast overnight, and one hour before surgery ranitidine 50 mg and metoclopramide 10 mg were administered intravenously. Inside the Operating room, the patient's identity was verified. Monitors attached. An intravenous cannulation was done with 18G cannula on the non-dominant forearm and co-loading started with 10 ml/kg Ringer lactate solution. Equipotent doses of the two vasopressor drugs were calculated based on the evidence available in the literature.<sup>6</sup> A potency ratio of 11.9:1 was calculated for phenylephrine and mephentermine and therefore doses of these two vasopressors were taken in a ratio of 1:12. Phenylephrine 2 mg or mephentermine 24 mg were diluted in 0.9% saline to make a total volume of 40 ml, resulting in a concentration of 50 mcg/ml of phenylephrine or 600 mcg/ml of mephentermine. The solutions of vasopressor for infusion were prepared by the investigator, patient was blinded to the identity of vasopressor used. After local infiltration, subarachnoid block was performed in sitting position, via L4-L5 interspace using a 25-gauge Quincke's needle (B. Braun Medical, Melsungen, Germany) while maintaining strict aseptic techniques and after establishing free flow of CSF 2.2mL of 0.5% hyperbaric bupivacaine (ANAWIN HEAVY 0.5%, NEON Inc, Mumbai, India) was injected in the patients. The patients were positioned supine and oxygen was administered by simple face mask. The upper level of sensory block was assessed in the midline with cotton soaked in spirit. Prophylactic infusion of vasopressor started at a rate of 60 ml/h (50 mcg/min for phenylephrine and 600 mcg/min for mephentermine) using a syringe infusion pump just after after confirming subarachnoid block. If hypotension (as defined above) occurred, a 1-ml bolus dose of the respective vasopressor solution (50mcg phenylephrine or 0.6 mg mephentermine) was administered through the infusion pump. If systolic blood pressure had exceeded >20% of the baseline SBP (hypertension) then infusion was stopped and again started when the value comes down to the less than or equal to baseline SBP. The aim was to maintain systolic blood pressure between the hypotension value and the baseline value. Bradycardia, if occurred, were managed by atropine. Hemodynamic parameters (SBP, DBP, MBP & HR) were monitored at 2 mins intervals till 16th min after that 3min interval were set till 40th mi. Oxytocin was given after delivery of baby according to "Rule of threes" i.e., 3 IU oxytocin intravenous loading dose(no faster than 15s) then 3 min assessment intervals, if inadequate uterine tone, give 3 IU oxytocin intravenous rescue dose again after 3min of assessment repeat the rescue dose. If the uterine tone is still inadequate the other pharmacological option includes ergonovine, carboprost, and misoprostol. After the operation over the patent was observe for 2hrs at recovery room and then transfer to ward.

## 2.2. Analysis of data

Statistical analysis has been performed using SPSS software (version 23.0; IBM Inc., Chicago, IL, USA, 2015). Continuous variables were compared between the two groups by unpaired Student's t-test. Ordinal data were analyzed using the Mann–Whitney non-parametric test. For qualitative data, either chi-square test or Fisher's exact test was used. Two factor, repeated measures ANOVA with one factor as a fixed group and the other as a repeated factor (i.e. time) was used to compare the variability between the subjects. Mauchly's test was used for checking sphericity. If found significant, the Greenhouse Geisser correction was used to find the p-value within time points. The value of  $p < 0.05$  was considered significant.

## 3. Results and Analysis

To begin with, describe the statistics for age (P:  $24.55 \pm 2.92$ ; M:  $26.50 \pm 4.32$ ). P-value found not to be significant. Body weight (P:  $59.85 \pm 5.39$ ; M:  $57.70 \pm 5.49$ ), P-value found not to be significant. Height between (P:  $153.75 \pm 4.16$ ; M:  $154.10 \pm 4.06$ ). P-value found not to be significant. Considering -operative hemodynamics baseline SBP, DBP, MBP and HR between group P and Group M P-value is found not to be significant. Applying statistical analysis paired T-test shows that the P-values within groups of the hypotensive episodes is found not to be statistically significant (Table 1). But Applying ANOVA between the groups shows the P-value is found to be statistically significant. (Table 3) comparison of heart rates between the two groups at different point of time and Applying statistical analysis ANOVA, p-value was found to be statistically significant at 12mins, 16mins, 19mins, 22mins, 25mins, 28mins, & 34 mins after giving spinal anesthesia. Looking into complication the incidence of reactive hypertension in the study groups and p-value is found to be not significant. There are more incidences of hypertension in the study group P than that of group M. incidence of bradycardia in the study groups is found not to be significant. The incidence of tachycardia in the study groups p-value is found not to be significant. The incidence of dyspnea in the study groups. P-value is found to be significant. Incidence of dyspnea is more in group M than that of group P. the incidence of headache in the study groups p-value is found not to be significant. The incidence of nausea & vomiting in the study groups p-value is found not to be significant

## 4. Discussion

Spinal anesthesia is preferred by most anesthesiologist for majority of cesarean section. The major advantage of the spinal anesthesia over the avoidance of maternal morbidity and mortality in associated with general anesthesia. Hypotension is the physiologic consequence of spinal anesthesia and can have a potentially deleterious maternal

and fetal impact.<sup>7</sup> Vasopressors, which lead to an increase in systemic vascular resistance and rise in mean arterial pressures,<sup>8</sup> have been traditionally used for the prevention and management of hypotension after neuraxial anesthesia. The results of our study suggest that phenylephrine and mephentermine both are effective in preventing maternal hypotension following spinal anesthesia Hypotension has been variously defined as a decrease in SBP of 30 mmHg,<sup>9</sup> a decrease of 20% below baseline systolic pressure<sup>10</sup> or an absolute value of  $< 100$  mmHg.<sup>11</sup> For the purpose of our study, hypotension was defined as a decrease in arterial pressure  $\geq 20\%$  from baseline SBP or  $< 100$  mmHg, whichever was higher. This was because the percentage decrease in placental perfusion is related to the percentage decrease in maternal arterial pressure and not to the absolute decrease in pressure. Moreover, a maternal SBP of  $< 100$  mmHg has been said to be responsible for 'pathologic foetal bradycardia. Groups developed hypotension; 8 out of 20 (40%) patients in phenylephrine group and 9 out of 20 (45%) patients in mephentermine had hypotension. Though number of patients developing hypotension in both the groups were not significantly different, but numbers of episodes of hypotension among patients of mephentermine group were 2.5 times more than those of phenylephrine group i.e. 32 episodes (Group-M) and 13 episodes (Group-P). There was significantly greater degree fall of blood pressure in patients of Group-M than Group-P in the number of patients who developed hypotension in both the group. Mean hypotensive SBP was  $87.91$  (SD=8.89) in Group-M and  $96.72$  (SD=3.93) was in Group-P. Thus, episodes of hypotension as well as decrease in SBP among these episodes were greater for mephentermine group than that of phenylephrine group. Thus, considering absolute values of hypotension, both groups are comparable in terms of preventing hypotension; however, phenylephrine had better control of maintenance over blood pressure than that of mephentermine in our study. Phenylephrine cause baroreceptor-mediated reflex bradycardia.<sup>12</sup> whereas mephentermine causes variable change in heart rate, depending on the degree of vagal tone. The CNS stimulating effects of mephentermine may result in tachycardia. We also encountered reactive hypertension in 3 patients (15%) in Group-P and had to stop phenylephrine infusion while no hypertension was noted in Group-M. Mohta et.al 2010,<sup>13</sup> infused phenylephrine @  $50\mu\text{g}/\text{min}$  and mephentermin @  $600\mu\text{g}/\text{min}$  and they reported bradycardia in 23% of patients in phenylephrine group and no patient had developed bradycardia in mephentermine group. We also encountered bradycardia 40% in phenylephrine group and 15% in mephentermine group and this is not statistically significant. The three patients who had developed reactive hypertension also had bradycardia. So out of eight patients who had developed bradycardia in Group-P the three patients were possibly

**Table 1:** Paired samples statistics

Grouping	Factor	Mean		N	Std. Deviation	Std. Error Mean
M	Pair 1	Baseline Blood Pressure	116.6667	9	8.87412	2.95804
		Average BP during Hypotensive Episodes	87.9111	9	8.89146	2.96382
P	Pair 1	Baseline Blood Pressure	118.2500	8	7.64853	2.70416
		Average BP during Hypotensive Episodes	96.7250	8	3.93945	1.39281

**Table 2:**

Grouping	Factor		N	Correlation	Sig.
M	Pair 1	Baseline Blood Pressure & Average BP during Hypotensive Episodes	9	.464	.208
P	Pair 1	Baseline Blood Pressure & Average BP during Hypotensive Episodes	8	.239	.569

Paired samples correlations and P-values

**Table 3:** ANOVA

Sum of Squares		df	Mean Square	F	
Baseline Blood Pressure	Between Groups	10.618	1	10.618	.153
	Within Groups	1039.500	15	69.300	
	Total	1050.118	16		
Average BP during Hypotensive Episodes	Between Groups	329.017	1	329.017	6.659
	Within Groups	741.099	15	49.407	
	Total	1070.116	16		

**Table 4:**

Baseline Blood Pressure	Between Groups	.701
	Within Groups	
Average BP during Hypotensive Episodes	Between Groups	.021
	Within Groups	

P-values of the hypotensive episodes between study groups.

due to reactive hypertension. And the rest of patients of Group-P and Group-M had bradycardia may be due to blockade of the thoracic sympathetic fibers (preganglionic cardiac accelerator fibers originating at T1-T5), as well as reflexive slowing of the heart rate as vasodilation reduces the venous return to the right atrium where stretch receptors respond by a compensatory slowing of the heart rate. Tachycardia (HR > 100) is seen 70% in phenylephrine group and 85% in mephentermine group. Spinal anesthesia and oxytocin induced hypotension are the possible causes of tachycardia in both the groups but CNS stimulating effect and more episodes of hypotension may be the cause of more prevalence of tachycardia in mephentermine group. When given as a rapid i.v. bolus, oxytocin causes hypotension and tachycardia.<sup>14</sup> The magnitude of these effects is dose-related. A low loading dose (ED 90 = 2.99 IU) is required in laboring women.<sup>15</sup> We had given 3 IU as bolus and repeated if necessary, as mentioned above to minimize hemodynamic changes. Oxytocin and release of aortocaval compression are the two major factors after delivery of baby

that alter the hemodynamics of mother. We minimized it by using low dose oxytocin. Twenty percent of patients in mephentermine and no patient in phenylephrine group had dyspnea. The intergroup difference is found to be statistically significant. Causes of dyspnea after spinal anesthesia include hypotension (causing hypoperfusion of the brainstem) and Other causes are the blunting of thoracic proprioception, the partial blockade of abdominal and intercostal muscles, and the recumbent position, which increases the pressure of the abdominal contents against the diaphragm. Other complication noted were headache and nausea and were found only in mephentermine group, but the intergroup difference is not significant. Anesthetic causes of intraoperative nausea and vomiting include hypotension (hypoperfusion to CTZ nuclei in brain) and increased vagal activity.

## 5. Conclusion

Considering absolute values of hypotension, both groups are comparable in terms of preventing hypotension; however,

phenylephrine had better control of maintenance over blood pressure than that of mephentermine. Reactive hypertension is common in phenylephrine infusion. Bradycardia is more prevalent in phenylephrine infusion than that of mephentermine while tachycardia is more common in mephentermine. Side effects like dyspnea, nausea/vomiting, headache is more common during hypotensive episodes. None of the drugs causes any untoward effect on fetus.

## 6. Source of funding

None.

## 7. Conflict of interest

None.

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