A Comparative Study of Bolus Phenylephrine and Mephentermine for Treatment of Hypotension during Spinal Anesthesia for Cesarean Section

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Citation

Abstract

Background: Cesarean section under spinal anesthesia is commonly associated with hypotension which can be detrimental to mother and fetus. It is the responsibility of the anaesthesiologist to ensure stable arterial blood pressure throughout surgery to avoid any decrease in maternal organ blood flow and placental insufficiency. Methods: Vasopressors are the cornerstone in treatment of hypotension during spinal anesthesia. Phenylephrine, [alpha]1 agonist and mephentermine, a direct and indirect acting sympathomimetic can be used to increase the arterial blood pressure. The current study aims to compare phenylephrine and mephentermine for maintenance of arterial blood pressure. Results: This study shows that both vasopressors can be used for the indication. The clinical outcomes like neonatal Apgar score, incidence of nausea and vomiting and other adverse events were comparable with both the vasopressors. Phenylephrine however has the advantage of decreased heart rate and requirement of lesser amount and more efficacy at maintaining the arterial blood pressure. The systolic blood pressure was significantly higher with phenylephrine 6 minutes after administration as compared to mephentermine. Conclusions: Mephentermine should be avoided in patients in whom increased heart rate may be undesired. Phenylephrine seems to be a better choice for the treatment of hypotension during spinal anesthesia for cesarean section.

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INTRODUCTION

Spinal anesthesia for cesarean section has several advantages over general anaesthesia like decreased risk of failed intubation, decreased risk of pulmonary aspiration of gastric contents, avoidance of the depressant effects of general anesthetics on neonate etc. Developments in regional anaesthesia have increased the relative risk of fatality during general anaesthesia for caesarean delivery to more than 16 times. 1

Single shot spinal is most commonly performed because it is simple, quicker, has faster onset with superior block and infrequent failure, lesser risk of systemic toxicity due to local anesthetic agent and lesser transfer to fetus as lower doses are used and its cost effectiveness. However, single shot spinal anesthesia has its own bag of adverse effects. The most common adverse effect is hypotension, primarily because of sympathectomy associated with the lumbosacral block. The incidence of hypotension during spinal anaesthesia is as high as 75-85%. 2 The clinical question of acceptable level of arterial blood pressure decrease after neuraxial block is acceptable remains to be answered. However, placental perfusion may be reduced in supine parturient even when mean arterial blood pressure is measured normal. 3 Hypotension during spinal anesthesia for cesarean delivery may thus further reduce it and may result in fetal acidosis, hypoxia and neurological injury besides maternal nausea and vomiting, dizziness and severe hypotension may result in loss of consciousness and sudden cardiac arrest. 4

Several pharmacologic and non-pharmacologic methods have been used for management of hypotension, with no single method adequate or conclusively superior. Amongst the vasopressors used (ephedrine, phenylephrine, metaraminol, mephentermine) none is conclusively better...
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over the other. 5

Although ephedrine has been used as the agent of choice, but the position has been challenged because of potential to cause supraventricular tachycardia (SVT), tachyphylaxis and fetal acidosis. 6

Recent studies favour phenylephrine, an \( \alpha \) agonist which elevates arterial blood pressure by increasing systemic vascular resistance secondary to vasoconstriction. Since the primary mode of hypotension during spinal anesthesia is vasodilation, it seems physiologic to use the vasoconstrictor. However, it causes bradycardia and serial dilution for i.v. administration is source of error. 7 It may cause uterine arteriolar constriction and thus diminishing uterine blood flow.

Mephentermine, which has mechanism of action similar to ephedrine, has been used for treatment of hypotension during spinal anesthesia. 8 Mephentermine is direct and indirect sympathomimetic action and probably the increase in arterial blood pressure is chiefly by increased cardiac output. This may be favourable for placental circulation.

The current study aims to compare bolus of the two vasopressors: phenylephrine and mephentermine as treatment of hypotension during spinal anaesthesia for cesarean section and add to evidence.

AIM AND OBJECTIVES

To compare phenylephrine and mephentermine for maintenance of the arterial blood pressure in women undergoing cesarean delivery under spinal anesthesia,

To compare effect of the two drugs on heart rate,

To compare effect of the two drugs on neurobehavior of the newborn,

To compare incidence of nausea, vomiting and other effects of the two.

INCLUSION CRITERIA

Singleton full term pregnant patients, age 20 to 35 years, of ASA grade I and II scheduled for elective cesarean delivery under spinal anesthesia, consenting to participate in the study at Burdwan Medical College & Hospital, Burdwan,

EXCLUSION CRITERIA

Patients having resting blood pressure more than 140/90 mm Hg, history of hypertension, pre-eclampsia/eclampsia, hyperthyroidism, and having coexisting neurologic, cerebrovascular, cardiovascular disorder (asymmetric septal hypertrophy, angina, etc), renal, metabolic, psychiatric disorder, glaucoma or occlusive vascular disorder were excluded. Those patients having history of hypersensitivity to local anaesthetic and any contraindications to spinal anaesthesia or having known fetal abnormalities were also not included.

Every the probable participant amongst the patients scheduled for elective caesarean delivery was explained about the study and a valid, written and informed consent was taken. This was done in the language and manner best suited for patient comprehension. Thus, the sample population was chosen from the population study in a simple random fashion.

Institution ethics committee approval was obtained prior to the conduct of the study.

MATERIAL AND METHODS

A recruitment target of 90 ( 45 in each group) was calculated to detect a difference of 6 mm Hg in systolic blood pressure (SBP) with 80% power of study and 5% probability of type I error. This calculation assumed a standard deviation of 10 mm Hg in this parameter within group. The participant was allocated to receive either i.v. bolus of phenylephrine 100 mcg or of mephentermine 6 mg to treat hypotension.

Hypotension was defined as a fall in systolic blood pressure to a value less than 80% of base value.

Inappropriate or severe bradycardia was defined as heart rate less than 60beats/min if the SBP was < 80% of base value, HR less than 50 beats/min when systolic blood pressure was above the value or heart rate less than 45 beats/min whatever the systolic blood pressure. 9

Study period was 3 hours after administration of spinal anesthesia.

PROCEDURE AND CONDUCT OF THE STUDY

The selected participant was advised oral ranitidine 150 mg on the night and on the coming morning. On the morning of surgery, the following data was obtained:

Body weight was taken to compare with earlier values and assess hydration. After intravenous cannulation with 18 gauge catheter, participant was infused Ringer lactate solution, 10 mL/kg BW rapidly which was continued thereafter at a rate of approximately 10-15 mL/min through out the study period. Three readings of systolic, diastolic
blood pressure and heart rate were obtained at three minutes of interval with patient at supine with a 15 degree wedge under right hip after the preloading. The lowest reading of blood pressure and highest reading of heart rate were taken as baseline values to minimize influence of anxiety in patients with high initial values. Highest Nausea and Vomiting Score value was taken as baseline. The participant was randomly allocated by sealed envelope method to receive bolus either phenylephrine 100 mcg or mephentermine 6 mg upon developing hypotension. The preparation of the study drugs for treatment of anticipated hypotension was done by an anesthesiologist blind to the study. The volume of each dose was equaled by adding 0.9% NaCl solution making the concentration of mephentermine 6 mg/mL and that of phenylephrine 100 mcg/mL. The identical syringes containing the solution were unlabeled and put in labeled tray.

Pulse oximeter probe, ECG electrodes, automated oscillometric blood pressure cuff, temperature probe was attached. The same, previously calibrated Multiple Parameter Monitor was used for all the participants and for all the readings including the baseline values. Fetal heart rate was monitored using stethoscope till the dressing and draping of the participant. No monitoring could be done thereafter till the delivery of fetus. Urinary catheterization was done with Foley’s urinary catheter.

Spinal anesthesia was administered with subarachnoid placement of bupivacaine 12.5 mg (2.5 mL of 0.5% bupivacaine with dextrose 8% solution) through the L3-L4 and L2-L3 interspinous spaces using 25 G Quinke needle. The patient was turned to supine position and after 5 min a 15° wedge was placed under the right flank. Dermatomal level of anaesthesia was assessed by loss of thermal discrimination to cold using ice cubes along mid-clavicular line 10 minutes after induction of anaesthesia. The target block height was equal to or above T8 and the surgeons was asked to proceed.

Oxygen was administered at a rate of 3L/min-1 by a face mask to all the patients until the umbilical cord was clamped. Inj. oxytocin 10U in 5% dextrose was given after clamping the cord. Participant was administered i.v. midazolam 0.02 mg/kg BW after the delivery of baby and shivering during the study was treated with i.v. tramadol 0.5mg/kg BW. Episode of nausea and vomiting was treated with i.v. ondansetron 4mg. Inappropriate or severe bradycardia was treated with bolus i.v. injection of atropine 0.3 mg.

Systolic, diastolic blood pressure was noted every 2 minutes after administration of spinal anaesthesia till next 20 minutes and every 5 minutes thereafter till the completion of surgery or at least 45 minutes and every 30 minutes for rest of study period. Heart rate and any cardiac rhythm disorder was monitored continuously using lead II. Nausea and vomiting and other maternal undesired effects were noted.

The time from intrathecal administration of bupivacaine to development of hypotension (SAB-Hypo), from spinal anaesthesia to delivery of baby (cord clamping) (SAB-Del) and duration of surgery (Dur-S) was noted.

The time to first repeat dose of the vasopressor and number of doses was noted.

Apgar score of the neonate for neurobehavioral assessment was noted at 1 and 5 minutes of delivery by attending paediatrician who was unaware of the vasopressor used.

The data collected were grouped at the end of whole trial depending on the type of vasopressor: Group P had participants who received phenylephrine while group M constituted those participants who had received mephentermine. The data of participants with successful spinal anaesthesia (defined as no need of intraoperative supplemental analgesic or conversion to general anaesthesia) and having incidence of hypotension and thus requiring vasopressor were included for statistical analysis of the study. The data of other participants like those which had failed spinal anaesthesia or those who did not develop hypotension were excluded as the aim of the study was to compare the effect of the two vasopressor and not to study the incidence of hypotension or failed spinal anaesthesia.

The numerical data were summarized by descriptive statistics (mean and standard deviation) and categorical data was summarized in terms of percentage. The numerical variables were compared between the groups by Student’s unpaired t-test and within the group by Wilcoxon Signed Rank Test analysis/ Student’s paired t-test and categorical data were compared between the groups by Chi-square test, Fisher’s exact test as appropriate. The analysis was two tailed with p<0.05 considered significant.

**OBSERVATIONS, RESULTS AND ANALYSIS**
Both the groups were comparable in their mean age, body weight and height with the difference in mean being not statistically significant (p>0.05) as analyzed using the Student’s unpaired t-test (two tailed).

The difference in block height between the groups was not statistically significant as analyzed by Chi-square test (p>0.05).

The baseline values of systolic, diastolic blood pressure and heart rate and the duration of surgery (Dur-S) was comparable between the groups with the difference in mean values being statistically not significant (p>0.05) as analyzed by Student’s unpaired t-test(two tailed).

* (Pearson χ², p=0.663).
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**Figure 7**
Table 5: The onset of hypotension (in minutes), and time of fetus delivery (in seconds) from administration of subarachnoid block (SAB) and the systolic, diastolic blood pressures (in mm Hg) and heart rate (in beats/min) at t (that is when hypotension occurred)

The systolic blood pressure, diastolic blood pressure and heart rate when SBP decreased by more than 20% was not statistically different between the two groups (p>0.05). The time to onset of hypotension after administration of spinal anaesthesia (SAB-Hypo) and time to delivery of the fetus (SAB-Del) was also comparable between the groups. These ratio variables were analyzed by Student’s unpaired t-test (two tailed) for difference in mean and p>0.05 was considered statistically insignificant.

![Table 5](image)

**Figure 8**
Table 6: Comparison of systolic blood pressures (mm Hg) at baseline value, 0, 2, 4, 6, 12 and 30 minutes after administration of the vasopressors

Analysis between the groups for difference in mean systolic blood pressure was done by Student’s unpaired t-test. There was no statistically significant difference between the two groups when vasopressor was administered i.e. 0 minute and at 2, 4, 12, and 30 minutes afterwards (p>0.05). However at 6 minutes after administration of the vasopressor, mean SBP in group P was significantly higher than that in group M [126.4444 ± 9.82473 vs 121.2889 ± 8.10337 (mean ± SD), p<0.05].
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Figure 9
Table 7: Wilcoxon Signed Rank Test analysis of SBP within the group

<table>
<thead>
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<th>Time points compared</th>
<th>p</th>
<th></th>
<th></th>
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<tr>
<td>Time points compared</td>
<td>Group P</td>
<td>Group M</td>
<td></td>
</tr>
<tr>
<td>0-basal, 2, 4, 6, 12, 30 minutes</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>2-basal</td>
<td>0.006</td>
<td>1.000</td>
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<tr>
<td>2-4 minutes</td>
<td>&lt;0.001</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>2-6 minutes</td>
<td>&lt;0.001</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>2-12 minutes</td>
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<td>0.766</td>
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<td>2-30 minutes</td>
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<td>0.222</td>
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<td>4-basal</td>
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<td>4-6 minutes</td>
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<tr>
<td>4-12 minutes</td>
<td>0.440</td>
<td>0.021</td>
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</tr>
<tr>
<td>4-30 minutes</td>
<td>0.055</td>
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<tr>
<td>6-basal</td>
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<tr>
<td>6-12 minutes</td>
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<td>6-30 minutes</td>
<td>0.001</td>
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<tr>
<td>12-basal</td>
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<td>12-30 minutes</td>
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<tr>
<td>30-basal</td>
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</table>

Statistical analysis of differences in mean SBP at different time points within the group was done by Wilcoxon Signed Rank Test. The increased mean SBP at 2, 4, 6, 12 and 30 minutes compared to the hypotensive (0 minute) value after administration of vasopressor was statistically significant in both the groups (p<0.001).

Within group P, the mean SBP at 2 minutes was less than the base value while more at 6 minutes (p<0.05). At 4, 12 and 30 minutes it was comparable to the base value (p>0.05).

As compared to 2 minutes, the SBP increased significantly at 4, 6 and 12 minutes (p<0.05). It became comparable at 30 minutes (p>0.05).

Within group M, the mean SBP was statistically not significant to base values at 2, 6, 12 and 30 minutes after administration of the vasopressor. However 4 minutes after administering the vasopressor there was statistically significant increased mean SBP compared to base value(p<0.05).

As compared to 2 minutes, the SBP increased significantly at 4 minutes (p<0.05). It became non-significant at 6, 12 and 30 minutes (p>0.05).

Figure 10
Figure 3: SBP at different time points after administration of vasopressor

Figure 11
Table 8: Comparison of diastolic blood pressures (mm Hg) at baseline, 0, 2, 4, 6, 12 and 30 minutes after administration of the vasopressors

The difference in mean diastolic blood pressure between the
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The difference in mean heart rate between the group was analyzed by Student’s unpaired t-test and at all the time points after administration of the vasopressors, HR was significantly higher in group M in comparison to group P (p<0.001).

Within group P, heart rate was significantly less at all time points after administration of the vasopressor (two tailed Student’s paired t-test, p<0.01) compared to the value at the time of hypotension and even when compared to the baseline value.

Within group M, heart rate was statistically non-significant at 2, 4, 6 and 12 minutes to that at hypotensive value (p>0.05), with significantly low mean at 30 minute (p<0.05). The mean HR at all time points was significantly higher at all time points after administration of the vasopressor when compared to baseline value (two tailed Student’s paired t-test, p<0.05).
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DISCUSSION
Management of hypotension during spinal anaesthesia is deemed necessary as organ blood flow is dependent on perfusion pressure.

\[ Q = \Delta P \times \left( \pi r^4 / 8 \mu L \right) \] (Hagen Poisseuille equation)

Where: 
- \( Q \) is the flow in small tubes (vessels)
- \( \Delta P \) is the pressure gradient
- \( r \) is the radius of the tube
- \( \mu \) is the viscosity of the liquid and
- \( L \) is the length of the tube

The current study was conducted to compare the two commonly used vasopressors for their efficacy at maintaining the arterial blood pressure. After the selection of the participants, they were allocated to receive i.v bolus of either phenylephrine 100 mcg. or mephentermine 6 mg on developing hypotension. The method of randomization was allocation by sealed envelope technique. Data was collected and the results were summarized and analyzed statistically by appropriate method.

The demographic data, baseline parameters were comparable in both groups. The hemodynamic parameters at the development of hypotension were also comparable between the groups. The mean time to development of hypotension after administration of spinal anaesthesia was 7.3778 ± 2.20834 (mean ± SD) minutes in group P and 6.9778 ± 2.47247 (mean ± SD) minutes in group M. The values were comparable with \( p=0.420 \).

After administration of the vasopressors, the SBP was comparable between the groups at all time points except at 6 minutes when the mean SBP was significantly higher in group P [126.4444 ± 9.82473 vs 121.2889 ± 8.10337 (mean ± SD), \( p<0.05 \)]. Sahu D and colleagues, however observed mean SBP to be statistically higher after 2 minutes when phenylephrine was the vasopressor in comparison to mephentermine [116.5 ± 14 vs 106.9 ± 11 (mean ± SD), \( p<0.05 \)]. The mean diastolic pressure was significantly higher in group P in comparison to group M at all time points after administration of vasopressor in the current study whereas it was observed to be comparable by Sahu D and colleagues.

The mean heart rate decreased significantly after administration of phenylephrine as compared to mean heart rate at the onset of hypotension whereas it remained high in group M and was statistically non-significant with values at the onset of hypotension till 30 minutes. Sahu D and colleagues reported similar findings in their study.

The primary mechanism of elevation of arterial blood pressure by phenylephrine is by vasoconstriction due to predominantly \( \alpha \) agonist activity whereas mephentermine increases MAP by augmenting cardiac output by increasing...
heart rate and myocardial contractility due to its \( \alpha \) and \( \beta \) agonist activity. The significant differences in diastolic blood pressure in the current study presumably reflect the predominantly \( \alpha_1 \) mediated vasoconstriction increased SVR due to phenylephrine. The persistent increased heart rate in group M is probably due to indirect as well as direct chronotropic effect of mephentermine.

Within the group analysis of SBP shows peak effect of phenylephrine to occur after 6 minute while that of mephentermine after 4 minutes.

The time to first repeat dose of vasopressor was comparable in both the groups. However mean number of doses was significantly more in group M. The sample size of the study might not have been large enough to avoid type II error in the comparison of this variable.

The incidence of nausea and vomiting and other effects was comparable between the two groups. The Apgar score at 1 and 5 minute was also statistically not significant between the groups.

The current study was limited in not being able to assess the end measures of adequacy of fetal circulation like umbilical artery flow velocity or umbilical artery pH. However this limitation was tried to overcome with assessment of Apgar score of the neonates.

We conclude from the study that both, phenylephrine and mephentermine maintain systolic blood pressure above hypotensive range, though phenylephrine might be better because number of doses needed is less and since phenylephrine increases diastolic blood pressure more than mephentermine and hence mean arterial pressure is increased. Thus, it can probably enhance organ blood flow more than mephentermine.

Mephentermine increases heart rate and thus may be avoided in population where the effect may be detrimental.

References
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