COMPARATIVE STUDY OF PHENYLEPHRINE, EPHEDRINE AND MEPHENTERMINE FOR TREATMENT OF HYPOTENSION DURING SPINAL ANESTHESIA FOR CAESAREAN SECTION

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ABSTRACT

**Background:** Hypotension is one of the commonest problems following Spinal anesthesia which may require vasopressors to maintain normal blood pressure. This study compares the efficacy of intravenous bolus doses of Phenylephrine, Ephedrine and Mephentermine for maintenance of blood pressure during Spinal anesthesia for Caesarean section.

**Materials & Methods:** Two hundred and fifty patients undergoing elective caesarean section who developed hypotension following spinal block were randomly allocated into three groups of 25 each. Group P-Phenylephrine 100µg, Group E- Ephedrine 6 mg, and Group M-Mephentermine 6 mg in 1 ml bolus intravenously.

**Results:** It was found that rise of Systolic blood pressure for first 6 minutes after administration of study drugs was significantly higher in group P compared to group E and group M (p<0.05). Similarly, elevation of Diastolic blood pressure in group P was significantly higher compared to other two groups for first 2 minutes. No significant differences were observed between changes in systolic and diastolic blood pressure of Ephedrine and Mephentermine group at any time. There was significant reduction in heart rate in Phenylephrine group but there was tachycardia following administration of Ephedrine and Mephentermine group at any time. There was no undue effect on the fetus in any group as assessed by neonatal APGAR scores.

**Conclusion:** All study drugs maintained blood pressure within 20% of baseline values on intravenous administration however rise in BP within first 6 minutes after bolus dose was significantly higher in phenylephrine group in comparison to ephedrine and mephentermine group. Correction of hypotension was better sustained in phenylephrine group. Moreover, Phenylephrine group causes significantly lower heart rate. There was no undue effect on the fetus in any group as assessed by neonatal APGAR scores.

Introduction

Spinal anesthesia for caesarean section has several advantages over general anesthesia like decreased risk of failed intubation, decreased risk of aspiration of gastric contents, avoidance of the depressant effects of general anesthetics on neonate etc.

Single shot spinal is most commonly performed because it is quicker, has faster onset with superior block and infrequent failure. However, single shot spinal anesthesia has some adverse effects also. The most common adverse effect is hypotension. The incidence of hypotension is as high as 75-85%.

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

Ephedrine is synthetic noncatecholamine that stimulates alpha and beta adrenergic receptors by indirect action as well as direct stimulating effects. It has been used as the agent of choice, but the position has been challenged because of potential to cause tachyphylaxis and fetal acidosis.

Recent studies favour Phenylephrine, a α1 agonist which elevates arterial blood pressure by increasing systemic vascular resistance secondary to vasoconstriction. However, it causes bradycardia. 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. Mephentermine is direct and indirect sympathomimetic action and probably the increase in arterial blood pressure is chiefly by increased cardiac output.

The present study was conducted to compare three vasopressors: Phenylephrine, Ephedrine and Mephentermine as treatment of hypotension during spinal anesthesia for caesarean section.

**Material and Methods**

The present prospective, randomized, double-blinded clinical study was conducted after obtaining permission from institutional ethical committee on 75 American Society of Anesthesiologists grade I-II patients with singleton, full term, uncomplicated pregnancy scheduled for elective caesarean section under spinal anesthesia. Patients with pregnancy-induced hypertension, history of diabetes, cardiovascular and cerebrovascular disease, fetal abnormalities and contraindication to spinal anesthesia were excluded from the study.

Informed written consent was taken from all patients. The patients were allocated to either of the three groups using computer generated random numbers. Group P(n=25) received Phenylephrine 100µg in 1ml iv bolus, Group E(n=25) received Ephedrine 6mg in 1ml iv bolus, and Group M(n=25) received Mephentermine 6mg in 1ml iv bolus.

Participants fasted overnight. On the morning of surgery, after intravenous cannulation with 18 gauge catheter, participant was preloaded with Ringer lactate solution, 10 mL/kg BW rapidly which was continued thereafter at a rate of approximately 15 mL/min throughout the study period. Three readings of systolic blood pressure, 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 heart rate was taken as baseline values to minimize influence of anxiety in patients with high initial values. Participants were randomly allocated by sealed envelope method to receive bolus either Phenylephrine 100 µg or Ephedrine 6 mg 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 Phenylephrine 100µg/ml, Ephedrine 6mg/ml and Mephentermine 6mg/ml. The identical syringes containing the solution were unlabeled and put in labeled tray.

Pulse oximeter probe, ECG electrodes, automated oscillometric blood pressure cuff were attached. Fetal heart rate was monitored using stethoscope till the painting and draping of the participant.

Spinal anaesthesia 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 interspinous spaces using 25 G Quinke...
needle under complete aseptic condition. The patient was turned to supine position and after 5 min a 15 cm wedge was placed under the right hip. Dermatome level of anaesthesia was assessed by loss of thermal discrimination to cold using ice cubes along mid-clavicular line 10 minutes after spinal anaesthesia. The target block height equal to or above T6 and the surgeons were asked to proceed.

Oxygen was administered at a rate of 3 L/min by a face mask to all the patients until the umbilical cord was clamped. Inj. oxytocin 10 U in 5% saline 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 0.5 mg/kg BW. Episode of nausea and vomiting was treated with i.v. ondansetron 4 mg. Bradycardia was defined as fall in heart rate below 50 beats per min and was treated with atropine 0.6 mg i.v.

Systolic blood pressure & diastolic blood pressure were 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 spinal anaesthesia to delivery of baby (SAB-Del) and from uterine incision to delivery of baby (UI-Del) were noted.

Hypotension was defined as a decrease in systolic arterial pressure > 20% of baseline values and it was treated by vasopressor. Total number of doses of vasopressor used was also 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.

**STATISTICAL METHOD**

Statistical analysis was done using Graph Pad InStat 3 software. Data were expressed as either mean and standard deviation or numbers and percentages. The means for the continuous variables were compared between the three groups using analysis of variance ANOVA. The P < 0.05 was considered statistically significant.

**RESULT**

All the patients who were enrolled in the study completed the study protocol and included in the data analysis. No spinal analgesia failure was observed. Demographic data & maternal and neonatal characteristics were comparable among all three groups [Table 1].

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group P</th>
<th>Group E</th>
<th>Group M</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.8±3.4</td>
<td>23.6±2.5</td>
<td>23.7±3.1</td>
<td>0.301</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.2±4.18</td>
<td>52.4±3.36</td>
<td>54.7±3.87</td>
<td>0.090</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>151.8±2.91</td>
<td>151.5±2.53</td>
<td>151.2±2.47</td>
<td>0.662</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>37.6±0.637</td>
<td>37.56±0.583</td>
<td>37.56±0.650</td>
<td>0.872</td>
</tr>
<tr>
<td>Weight of neonate (kg)</td>
<td>2.86±0.222</td>
<td>2.86±0.250</td>
<td>2.80±0.232</td>
<td>0.663</td>
</tr>
<tr>
<td>SA to delivery (min)</td>
<td>8.21±1.092</td>
<td>8.24±1.026</td>
<td>8.84±1.772</td>
<td>0.272</td>
</tr>
<tr>
<td>UI to delivery (sec)</td>
<td>2.08±0.276</td>
<td>2.32±0.556</td>
<td>2.52±0.918</td>
<td>0.057</td>
</tr>
<tr>
<td>Block height at skin incision (dermatome) *</td>
<td>T4 (T4,T5)</td>
<td>T4 (T4,T5)</td>
<td>T4 (T4,T5)</td>
<td></td>
</tr>
</tbody>
</table>

Baseline mean heart rate was statistically comparable in all three groups. Heart rate increased in all three groups during hypotension. On intergroup comparison, post drug administration, heart rate was significantly less in group P as compared to Group E and Group M till 25 min (P<0.05), after that it was not significant (P>0.05). No significant differences were observed between Group E and Group M (P>0.05) [Table 2].

Baseline mean systolic blood pressure was statistically comparable in all three groups. There was fall in systolic blood pressure in all the three groups during hypotension. On intergroup comparison, post drug administration, rise of systolic blood pressure at 2.4 and 6 min were significantly less in Group E and Group M as compared to Group P (P<0.05) after 6 min it was not significant (P>0.05). No significant differences were observed between Group E and Group M (P>0.05) [Table 3].

Baseline mean diastolic blood pressure was statistically comparable in all three groups. There was fall in diastolic blood pressure in all the three groups during hypotension. On intergroup comparison, post drug administration, rise of diastolic blood pressure at 2 min was significantly less in Group E and Group M as compared to Group P (P<0.05) after that it was not significant (P>0.05). No significant differences were observed between Group E and Group M (P>0.05) [Table 4].

Group P 72% required single bolus dose while 28% required two bolus doses to maintain systolic blood pressure within 20% limit of basal value. In Group E 56% required single, 40% two and 4% three bolus doses, whereas In Group M 64% required single, 28% two, and 8% three doses to maintain systolic blood pressure within 20% limit of basal value [Table 5].

Apgar score at 1 minute was 6.16, 6.12 and 6.20 in group P, group E and group M respectively. Apgar score at 5 min was 8.04, 8.12 and 8.16 in group P, group E and group M respectively. No significant difference was observed between the three groups (P>0.05) [Table 6].

There were 12% cases of nausea and vomiting in group P, 16% cases of nausea and vomiting in group E and 12% cases of nausea and vomiting in group M. In Group P 12% of patients developed bradycardia and no patient developed bradycardia in group E and 12% cases of nausea and vomiting in group M. In group P 12% of patients developed bradycardia and no patient developed bradycardia in group E and group M [Table 7].


DISCUSSION

The demographic data, baseline parameters were comparable in both groups. The hemodynamic parameters at the development of hypotension were also comparable between the groups. Vasopressor was given at the onset of hypotension in all the three groups. Rise in systolic blood pressure and diastolic blood pressure was found in all the three groups.

On intergroup comparison, post drug administration, rise of systolic blood pressure at 2.4 and 6 min & rise of diastolic blood pressure at 2 min were significantly less in Group E and Group M as compared to Group P (p<0.05), after that it was not significant for the rest of the observation period (p>0.05). No significant differences were observed between Group E and Group M (p>0.05). Our results are comparable with the results of study done by Sahu D et al.6

Hypotension due to spinal anaesthesia is caused due to various factors. Mesenteric vasodilation along with partial caval compression leads to decreased venous return. The decreased cardiac output thus caused is further accentuated by the decreased in heart rate. Ephedrine and Mephentermine has predominant β-agonist activity and hence causes restoration of blood pressure mainly by increase in cardiac output and heart rate. Phenylephrine, on the other hand, has predominant α-agonist activity and restores the blood pressure by virtue of peripheral vasoconstriction and increase in venous return to the heart.

The baseline mean heart rate was similar in all the three groups. There was rise in mean heart rate from the baseline at the onset of hypotension in all groups. On intergroup comparison, post drug administration, heart rate was significantly less in Group P as compared to Group E and Group M till 25 min (p<0.05), after that it was not significant (p>0.05). No significant differences were observed between Group E and Group M (p>0.05). The significant decrease in mean heart rate in Phenylephrine group as compared to Ephedrine and Mephentermine groups in our study is comparable with the results of study done by Sahu D et al.6

The observations made above can be explained on the mechanism of the actions of Phenylephrine, Ephedrine and Mephentermine. Mephentermine and Ephedrine have predominantly β-agonist activity. Therefore, they are expected to cause increase in heart rate. On the other hand, phenylephrine, with predominant α-agonist action, causes a rise in the arterial blood pressure without any direct effect on the heart rate. This leads to activation of baroreceptor reflex and subsequent decrease in heart rate indirectly.

There were 12 % cases of bradycardia required atropine in Phenylephrine group as compared to no case of bradycardia in Ephedrine and Mephentermine. Our results are similar with the study done by Thomas DG et al.8 More than 50% of women given Phenylephrine in their study developed significant bradycardia.

Bradycardia could be caused by cardiac sympathetic denervation associated with high spinal block or a secondary baroreflex response to vasopressor induced hypertension. As Ephedrine and Mephentermine are associated with β-agonist activity, bradycardia may be masked by the tachycardia induced by Ephedrine. Phenylephrine, on the other hand, is devoid of any β-agonist activity and can be associated with bradycardia.

Apagar score at 1 min and 5 minute did not show any difference between the groups (p>0.05). Apagar score was normal in all the

Table 5 Number of bolus dose of vasopressor required in various groups

<table>
<thead>
<tr>
<th>No of bolus</th>
<th>Group P</th>
<th>Group E</th>
<th>Group M</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 (72%)</td>
<td>14 (56%)</td>
<td>16 (64%)</td>
</tr>
<tr>
<td>2</td>
<td>7 (28%)</td>
<td>10 (40%)</td>
<td>7 (28%)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

Table 6 Apgar score

<table>
<thead>
<tr>
<th>APGAR score</th>
<th>Group P</th>
<th>Group E</th>
<th>Group M</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1min</td>
<td>6.16±0.850</td>
<td>6.12±0.725</td>
<td>6.20±0.707</td>
<td>0.933</td>
</tr>
<tr>
<td>5min</td>
<td>8.04±0.675</td>
<td>8.12±0.665</td>
<td>8.16±0.624</td>
<td>0.805</td>
</tr>
</tbody>
</table>

Table 7 Incidence of Side Effects

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Group P</th>
<th>Group E</th>
<th>Group M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea &amp; Vomiting</td>
<td>3 (12%)</td>
<td>4 (16%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Shivering</td>
<td>4 (16%)</td>
<td>3 (12%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>3 (12%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
neonates in all three groups and there was no case of neonatal depression.

The incidence of nausea and vomiting and other effects was comparable between the two groups. The current study was limited in not being able to assess umbilical artery pH. However this limitation was tried to overcome with assessment of Apgar score of the neonates.

Conclusion
We conclude from the above study that all the three drugs maintained arterial blood pressure within 20% limit of baseline values on intravenous bolus administration without any undue effect on mother and fetus, although rise in BP within first 6 min after bolus dose was significantly higher in Phenylephrine group in comparison to Ephedrine and Mephentermine group. Correction of hypotension was better sustained in Phenylephrine group and it also causes reduction in heart rate, which may be advantageous in cardiac patients and patients in whom tachycardia is undesirable. Hence, it may be inferred that bolus Phenylephrine may be better alternative to Ephedrine and Mephentermine as a vasopressor agent for treatment of hypotension in women undergoing caesarean section under spinal anaesthesia.

References