A COMPARISON OF PRE-EMPTIVE INTRAMUSCULAR PHENYLEPHRINE AND EPHEDRINE IN PREVENTION OF SPINAL ANAESTHESIA INDUCED HYPOTENSION DURING CAESAREAN SECTION

Sunil Raskaran¹, Neelesh Nema², Mahendra Mujalde³, Kumar Mrinal⁴, Jitendra Verma⁵, Nitin Mantri⁶, Sachin Kumbhare⁷

HOW TO CITE THIS ARTICLE:

ABSTRACT: OBJECTIVE: sub arachnoid block is extensively used for the conduction of caesarean section without prophylactic measures; hypotension is a frequent occurrence (in about 80% of the patients). Hypotension is associated with distressing symptoms of dizziness, nausea and vomiting, and may also interfere with the surgical procedure. Present study is a comparison of pre-emptive intramuscular phenylephrine and ephedrine in prevention of spinal anesthesia induced hypotension during caesarian section. METHODS: In this randomized double blind, placebo controlled study, we have evaluated preemptive phenylephrine 2 mg IM; in comparison with ephedrine 45 mg IM and 2 ml saline given just after induction of spinal anesthesia, in terms of hemodynamic stability, development of symptoms like nausea and vomiting and requirement for rescue IV ephedrine vasopressor therapy in patients undergoing lower segment caesarean section. RESULTS: All the groups were comparable with respect to mean age, mean body weight MAP, and mean Pulse rate. In conclusion, pre-emptive use of intramuscular phenylephrine and ephedrine was found to be effective in prevention of spinal anesthesia induced hypotension, nausea and vomiting significantly. However, statistically no difference (p=0.351) was found between the phenylephrine and ephedrine group although the incidence of hypotension, nausea and vomiting was less in phenylephrine group. CONCLUSION: Phenylephrine group seems better to prevent incidence of hypotension, nausea and vomiting among all groups.

KEYWORDS: Phenylephrine, ephedrine, MAP, Pulse Rate.

INTRODUCTION: Regional anesthesia in the form of epidural or subarachnoid block is extensively used for the conduction of caesarean section and gynecological lower abdominal surgeries. Without prophylactic measures, hypotension is a frequent occurrence (in about 80% of the patients) during spinal anesthesia (Rout CC et al 1993).1 Hypotension is associated with distressing symptoms of dizziness, nausea and vomiting, and may also interfere with the surgical procedure.2 Ideally hypotension should be prevented in patients receiving spinal anesthesia.

Prophylactic intravenous hydration has been used as first line measure to prevent hypotension although the place of preloading is now being questioned (Jackson R et al 1995).2 The management of choice, however, if hypotension occurs is the use of vaspressors as required The usual approach to the use of vaspressors in this clinical setting is reactive rather than proactive; spinal anesthesia induced hypotension is allowed to develop and is then treated accordingly.

In this randomized double blind, placebo controlled study, we have evaluated preemptive phenylephrine 2 mg IM; in comparison with ephedrine 45 mg IM and 2 ml saline (IM) given just after induction of spinal anesthesia, in terms of hemodynamic stability, development of symptoms like...
nausea and vomiting and requirement for rescue IV ephedrine vasopressor therapy in patients undergoing lower segment caesarean section.

**METHODOLOGY:** After obtaining approval from the Hospital Ethics Committee and written informed consent from the patients, this single Centre, prospective, randomized, double blind study was conducted in the Department of Anesthesiology MGM Medical College, Indore. A sample size of 90 patients with ASA Grade I and II aged between 20 to 35 years and height more than 150 cm undergoing elective caesarean section under spinal anesthesia. They were randomly divided into three equal groups, Group 1 (C), 2 (M) and 3 (P).

Each patient underwent a thorough pre-anesthetic checkup prior to the procedure. This study was designed to evaluate preemptive phenylephrine 2 mg IM; in comparison with ephedrine 45 mg IM and 2 ml saline (IM) given just after induction of spinal anesthesia, in terms of hemodynamic stability, development of symptoms like nausea and vomiting and requirement for rescue IV ephedrine vasopressor therapy in patients undergoing lower segment caesarean section.

Patients who were unwilling, posted for emergency surgeries, any significant medical history, otherwise contraindicated for spinal anesthesia, those allergic to amide local anesthetic or any other drug, ones with a history of drug or alcohol abuse and obese patients (those with body mass index >29 kg/m\(^2\)) were excluded from the study. Before the commencement of anesthesia, patients were informed about the procedure.

**The patients were randomly divided into 3 groups:**

- Group 1 - Received 2 ml saline 0.9% IM (C)
- Group 2 - Received ephedrine 45 mg IM (E)
- Group 3 - Received phenylephrine 2 mg IM (P)

Randomization was done by putting 90 paper chits in a box containing 30 chits each of C, E, and P groups. Each patient in the study was asked to randomly pick any chit and was allotted that respective group. Double blinding was done by giving responsibility of observation and drug injection to two different persons.

Non-invasive blood pressure and heart rate reading were taken 3 times at 2 minutes interval and the lowest blood pressure and heart rate recording were taken as baseline. (The lowest MAP value was chosen to minimize the influence of anxiety). An 18-gauge IV cannula was cited in the non-dominant hand and 500 ml of Ringer's lactate solution was given as a preload. Spinal anesthesia was given in sitting position at L2-3 or L3-4, with a 25G quincke spinal needle using median approach taking full aseptic precautions.

The spinal injection contained 2.5 ml of Bupivacaine 0.5% heavy, the patient was then placed in supine position, with a 15° left lateral tilt. The IM injection of the study medication was given into the left deltoid muscle immediately after the subarachnoid injection. The time of IM injection was taken as time zero. Vital parameters (pulse, non-invasive blood pressure, SpO2) and symptoms (nausea, vomiting) were monitored every 5 minutes till 60 minutes after spinal injection. Rescue intravenous bolus doses of ephedrine (6 mg) were to be given if the patient developed hypotension, nausea or vomiting. Injection glycopyrrolate (0.2 mg) was given if the patient developed bradycardia intraoperatively.
Hypotension was defined as a 25% decrease in mean arterial pressure (MAP) from baseline. The percentage change in MAP was calculated from the difference between baseline and the lowest recorded MAP, which occurred within the study period. The baseline heart rate was taken as the lowest recorded heart rate before administration of the study drug. Heart rate below 50 beats/minute was taken as bradycardia and above 120 beats/minute was taken as tachycardia.

Hemodynamic data, and physical characteristics were compared using analysis of variance with Dunnet’s post-hoc test for difference between the groups compared with control. Categorical data, incidence of hypotension and incidence of use of rescue ephedrine therapy were compared after constructing table and applying the chi-squared test or Fischer’s exact test as appropriate.

**OBSERVATIONS & RESULTS:**

<table>
<thead>
<tr>
<th>Age group (yrs)</th>
<th>Group C</th>
<th>Group E</th>
<th>Group P</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-25</td>
<td>20</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>26-30</td>
<td>10</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>31-35</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>30</strong></td>
<td><strong>30</strong></td>
<td><strong>30</strong></td>
</tr>
</tbody>
</table>

Table 1: Demography of each age group of patients

<table>
<thead>
<tr>
<th></th>
<th>Group C</th>
<th>Group E</th>
<th>Group P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs) (mean±SD)</td>
<td>24.06±2.72</td>
<td>24.53±3.30</td>
<td>24.53±2.87</td>
</tr>
<tr>
<td>Body wt (Kgs) (mean±SD)</td>
<td>59.06±4.56</td>
<td>58.33±4.34</td>
<td>58.33±5.11</td>
</tr>
<tr>
<td>Baseline MAP (mm of Hg)</td>
<td>89.73±6.19</td>
<td>89.9±4.97</td>
<td>88.1±4.88</td>
</tr>
<tr>
<td>Baseline Pulse/min.</td>
<td>92.8±10.06</td>
<td>94.13±11.83</td>
<td>92.1±12.88</td>
</tr>
<tr>
<td>No.(n) of patients with hypotension</td>
<td>19</td>
<td>08</td>
<td>05</td>
</tr>
<tr>
<td>Percentage of patients with hypotension</td>
<td>63</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>No. (n) Of patients with nausea, vomiting (%)</td>
<td>8(27%)</td>
<td>2(7%)</td>
<td>0(0%)</td>
</tr>
<tr>
<td>Episodes of rescue ephedrine requirement</td>
<td>27</td>
<td>10</td>
<td>07</td>
</tr>
</tbody>
</table>

Table 2: Mean (age, body weight, baseline MAP and baseline Pulse). Incidence of hypotension, nausea, vomiting and total episodes of rescue IV ephedrine requirement

MAP (mean arterial pressure) = (SBP+2DBP)/3 = DBP+1/3PP.
Hypotension = decrease in MAP by >25% of baseline MAP.

<table>
<thead>
<tr>
<th></th>
<th>Group C&amp;E</th>
<th>Group C&amp;P</th>
<th>Group E&amp;P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>P Value</td>
<td>0.5495</td>
<td>0.5176</td>
</tr>
<tr>
<td></td>
<td>Significance</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
<tr>
<td>Mean body weight</td>
<td>P Value</td>
<td>0.5278</td>
<td>0.5616</td>
</tr>
<tr>
<td></td>
<td>Significance</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
</tbody>
</table>
### Table 3: Comparison of various groups

<table>
<thead>
<tr>
<th></th>
<th>P Value</th>
<th>0.9070</th>
<th>0.0848</th>
<th>0.1623</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MAP</td>
<td>Significance</td>
<td>Not significant</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
<tr>
<td>Baseline pulse rate</td>
<td>P Value</td>
<td>0.6408</td>
<td>0.8153</td>
<td>0.5274</td>
</tr>
<tr>
<td>Incidence of hypotension</td>
<td>P Value</td>
<td>0.005</td>
<td>0.000</td>
<td>0.351</td>
</tr>
<tr>
<td>Incidence of nausea, vomiting</td>
<td>P Value</td>
<td>0.039</td>
<td>0.003</td>
<td>0.154</td>
</tr>
<tr>
<td>Episodes of rescue ephedrine requirement</td>
<td>P Value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.394</td>
</tr>
</tbody>
</table>

1. It was observed that mean age and body weight was similar in all the groups and no statistically significant difference was present.

2. Maximum hypotension was observed in control group. As compared to the control group, incidence of hypotension was significantly less in phenylephrine group as well as ephedrine group. Also comparing ephedrine and phenylephrine groups, although incidence of hypotension was low in phenylephrine group but it was not found to be significant.

3. Maximum incidence of nausea and vomiting was observed in control group. As compared to control group, incidence of nausea, vomiting was significantly less in ephedrine as well as phenylephrine group. The incidence of nausea and vomiting was nil in ephedrine group but it was not statistically significant in phenylephrine group. Patients who experienced hypotension and its complications (nausea, vomiting) were treated with single IV bolus of ephedrine (6 mg).

4. All the patients who developed hypotension, nausea or vomiting were given rescue ephedrine 6 mg IV. Many patients required more than one dose of rescue ephedrine to treat hypotension, nausea or vomiting. Maximum episodes of rescue ephedrine administration were observed in control group. In comparison with control group, episodes were significantly less in ephedrine as well as phenylephrine group. Also among ephedrine and phenylephrine groups, the difference between phenylephrine and ephedrine group was not found to be significant.

**DISCUSSION:** Ideally hypotension should be prevented in patients receiving spinal anesthesia. Prophylactic intravenous hydration has been used as first line measure to prevent hypotension although the place of preloading is now being questioned (Jackson R et al 1995). The management of choice, however, if hypotension occurs is the use of vasopressors as required.

In this randomized double blinded, controlled study, 90 patients (20-35 years) undergoing elective caesarean section were evaluated for incidence of hypotension and its side effects (nausea, vomiting) after administration of spinal anesthesia. They were divided in three groups namely, group C, group E, group P. Each group received prophylactic intramuscular saline 0.9 % (group C), ephedrine 45 mg (group E) and phenylephrine 2mg (group P).

The intraoperative episodes of hypotension, nausea and vomiting were treated with ephedrine 6 mg IV bolus (rescue ephedrine). All the groups were similar demographically and mean age and body weight among the groups were also found to be similar statistically.
Spinal anesthesia administration, Hypotension is defined arbitrarily in most studies, with values ranging from a 20-30% reduction from baseline systolic arterial pressure (SAP) to absolute values less than 90-100 mmHg (Rout CC et al 1993, Jackson R et al 1995, Webb AA et al 1998). The trigger for rescue IV ephedrine use in this study was not only a 25% reduction in MAP, but also the presence of nausea, vomiting.

Hence, it was observed that there was requirement for some rescue IV ephedrine therapy in all the groups. The data demonstrated a reduction in the incidence of nausea, vomiting as well as episodes of rescue ephedrine required. The lowest MAP (mean arterial pressure) value and pulse rate in the 3 readings at 2 minutes interval was chosen to allow anxious patients to settle and avoid spuriously high MAP and pulse rate values, which might have influenced the baseline measurement.

In this study, the effect of vasopressors, given before the onset of hypotension was observed, and a therapeutically useful effect found. The place for IV vasopressors for treatment of hypotension during spinal anesthesia is well established. However, giving IM vasopressors before a spinal anesthesia is more controversial because of concerns about reactive hypertension. A study comparing ephedrine 37.5 mg IM, with placebo showed improved cardiovascular stability in the ephedrine group, but with a persistent 50% incidence of hypotension (Webb AA et al 1998).

Sternlo and colleagues found ephedrine 0.6 mg/kg, was effective in reducing the incidence of hypotension in patients undergoing hip arthroplasty under spinal anesthesia (Sternlo JE et al 1995). Ayorinde BT et al (2001) showed that the pre-emptive IM phenylephrine 4 mg and ephedrine 45 mg reduce the severity of hypotension and the total dose of rescue IV ephedrine during spinal anesthesia for caesarean section.

In the present study 2 mg phenylephrine(P), 45 mg ephedrine(E) and 0.9% saline was administered intramuscularly just after the induction of spinal anesthesia in patients undergoing elective caesarean section. Although, a reduction was seen in the incidence of spinal anesthesia induced hypotension with IM vasopressor therapy, there was still some incidence of hypotension.

Pharmacokinetic studies have suggested that the peak effect of IM phenylephrine or ephedrine is 15-20 minutes after administration (ABPI Compendium 1999-2000). Therefore, to circumvent the concerns about reactive hypertension and other side effects associated with IM vasopressor administration, the spinal block was given just before the intramuscular injection of test drug.

**INCIDENCE OF HYPOTENSION:** Ephedrine causes restoration of blood pressure mainly by increasing heart rate and contractility (direct β-agonist activity) and also by producing some vasoconstriction (indirect effect) (Critchley LAH et al 1995). Phenylephrine on the other hand, has predominant α-agonistic activity and restores the blood pressures by virtue of arterial as well as venous vasoconstriction, leading to increase in both systemic vascular resistance and venous return to the heart.

Hypotension in this study was taken as decrease in MAP by >25% of baseline MAP. It was observed that incidence of hypotension was significantly less in phenylephrine (16%) and ephedrine (26%) groups as compared to control group (63%) (p<0.05). Comparing the incidence of hypotension in phenylephrine group and ephedrine group, although incidence of hypotension was low in phenylephrine group but it was not found to be significant. (p=0.351)
In the study done by Ayorinde BT et al (2001), they found that incidence of hypotension was significantly less in phenylephrine 4mg (33%) as compared to control group (70%). Also they found that incidence of hypotension in phenylephrine 4 mg group was 33% as compared to ephedrine 45 mg which had an incidence of 48%, and this difference was not significant statistically.

Our study have also showed similar results in the incidence of hypotension in phenylephrine group (16%) as compared to ephedrine group (26%) (p=0.351). In the study by Kohki Nishikawa and associates (2002), they found that prophylactic intramuscular administration of phenylephrine 1.5 mg and 3 mg in elderly patients >65 yrs resulted in significant reduction in incidence of hypotension (p<0.01). They also observed hypertension after the test drug administration in phenylephrine 3 mg group, that’s why we have given 2 mg phenylephrine instead of more dose.

INCIDENCE OF NAUSEA AND VOMITING: The hypotension that accompanies spinal anesthesia is often heralded by nausea and vomiting. Possibly by reduction in medullary blood flow to chemoreceptor trigger zone. Vasopressor drugs increase mean arterial pressure and presumably medullary blood flow as well, thus reducing these symptoms. Patients who developed nausea and vomiting intra-operatively were treated with rescue ephedrine 6 mg IV.

A significant reduction in incidence of nausea, vomiting was observed in phenylephrine (0) and ephedrine (2) groups as compared to control group (8) (p=<0.05). Also the incidence of nausea and vomiting was less in phenylephrine group as compared to ephedrine group but it was not found to be statistically significant (p=0.154). This finding is in corroboration with incidence of hypotension among the groups.

It was so expected because nausea, vomiting in these patients occurred mainly as a complication of spinal anesthesia only. Cooper DW et al (2002) also found that giving phenylephrine alone by infusion at caesarean delivery was associated with a lower incidence of maternal nausea and vomiting than giving ephedrine alone.

RESCUE EPHEDRINE 6 MG IV: All the patients who developed hypotension, nausea, vomiting intra-operatively were given 6 mg ephedrine IV (rescue ephedrine).Episodes of ephedrine administered were significantly less in phenylephrine group (7) as compared to ephedrine (10) and control (27) groups, (p<0.05).

The response to ephedrine administration was seen as an increase in blood pressure and pulse rate and relief from distressing symptoms from nausea and vomiting (if present). The response was seen to be similar in all the three groups. None of the patients developed hypertension (>25% increase from baseline MAP) and /or tachycardia (heart rate>120 beats per minute).

Some patients require a second dose of rescue ephedrine as their symptoms were not completely treated by the first dose. Time of first dose of rescue was found to be around 5 min after spinal administration in control (C) and ephedrine group (E) but it was around 15 min after spinal administration in phenylephrine group (P).

Ayörinde BT et al (2001) also observed that phenylephrine 4 mg and ephedrine 45 mg groups required significantly lower doses of rescue IV ephedrine as compared to control group (p=0.02). They also observed that the time to first requirement for rescue IV ephedrine therapy was also similar between the two groups.
PULSE RATE: Ephedrine due to its predominantly β-agonist activity is expected to cause an 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 the heart rate indirectly. Bradycardia could also be caused by cardiac sympathetic denervation associated with high spinal block.

None of the patients in the present study developed tachycardia but 2 patients in the phenylephrine group developed bradycardia for which IV glycopyrolate was given. In the study by Kohki Nishikawa and associates (2002), bradycardia (heart rate< 50bpm) after IM administration of phenylephrine was not observed in any of the groups. Also none of the patients in any group developed bradycardia in the study done by Ayorinde BT et al (2001). In both of these studies phenylephrine and ephedrine were administered IM prophylactically.

Bradycardia was observed in various studies in patients receiving IV bolus or infusion of phenylephrine either prophylactically or therapeutically. (Dinesh Sahu et al 2003, Ngan Kee WD et al 2004). So it was found that prophylactic intramuscular administration of phenylephrine 2 mg and ephedrine 45 mg reduce the incidence of hypotension, nausea, vomiting and total episodes of rescue IV ephedrine therapy during spinal anesthesia but these effects were more in patients receiving IM ephedrine as compared to IM phenylephrine.

Also no adverse effect was seen in phenylephrine group except bradycardia as compared to ephedrine group. In conclusion, prophylactic use of both phenylephrine & ephedrine used intramuscularly were effective in prevention of side effects like hypotension, nausea and vomiting after spinal anesthesia administration. The incidence of hypotension, nausea, vomiting was less in phenylephrine group as compared to ephedrine group but still the difference was not found to be statistically significant. (p = 0.351).

SUMMARY & CONCLUSION: This randomized, double blinded, controlled study was conducted in the department of anesthesiology, MGM Medical College & MY Hospital, Indore. 90 patients meant to undergo elective lower segment caesarean section under spinal anesthesia were chosen.

The patients were randomly divided in three Groups:
- **Group 1** – Received saline 0.9% IM (C).
- **Group 2** – Received ephedrine 45 mg IM (E).
- **Group 3** – Received phenylephrine 2 mg IM (P).

In conclusion, pre-emptive use of intramuscular phenylephrine and ephedrine was found to be effective in prevention of spinal anesthesia induced hypotension, nausea and vomiting. However, statistically no difference (p=0.351) was found between the phenylephrine and ephedrine group although the incidence of hypotension, nausea and vomiting was less in phenylephrine group.

BIBLIOGRAPHY:


Fig. 1: Age Distribution
Fig. 2: Mean age and body weight

Fig. 3: Baseline MAP and Pulse
Fig. 4: Total episodes of rescue IV ephedrine requirement in the three groups

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