COMPARISON BETWEEN TWO DIFFERENT DOSES OF NOREPINEPHRINE INFUSION FOR PREVENTING POST SPINAL ANESTHESIA HYPOTENSION DURING CESAREAN SECTION

Rupak Bhattarai, Amarendra Kumar Yadav, Parasmani Shah, Prabin Sharma

ABSTRACT

Introduction
Post spinal maternal hypotension is a common complication during cesarean section. Norepinephrine is a vasopressor recently used in obstetrics anesthesia. However, there are less data available regarding its optimal dose.

Objective
The main objective of this study is to compare two doses of infusion of norepinephrine for post spinal hypotension during cesarean delivery.

Methodology
A prospective, randomized, double blinded study on full term pregnant patient scheduled for elective cesarean delivery. The infusion of Norepinephrine started after spinal anesthesia and the patient was randomly divided into two groups. Group A received norepinephrine infusion rate of 0.025ug/kg/min and Group B received at a rate of 0.050ug/kg/min. The norepinephrine was continued till 5 minutes after the delivery of fetus and subsequently stopped. These two groups were compared with systolic blood pressure, mean arterial pressure, heart rate, intraoperative hypotensive episodes, Nausea and Vomiting, tachycardia and neonatal outcomes.

Result
Systolic blood pressure and mean arterial pressure was higher in group B when compared with group A at all time intervals intraoperatively. The minimum systolic blood pressure and mean arterial blood pressure in group A were 91.61±8.76 and 59.8±5.29 and group B were 90.67±1.21 and 65±3.46 respectively. No significant difference in heart rate between the two groups. In 0.025ug/kg/min group had 23 (46%) hypotensive episode whereas in 0.050ug/kg/min group had 6 (12%) hypotensive episodes (p<0.001). In group A 9 patient had nausea and vomiting. Bradycardia was seen in 2% of patients in group A. Tachycardia was seen in 4% of patients in group B. Apgar score was comparable and significant (P<0.05) in 10 minutes.

Conclusion
In the present study, the infusion of 0.050ug/kg/min norepinephrine reduced the hypotensive episodes when compared with the infusion of 0.025ug/kg/min norepinephrine following spinal Anesthesia during cesarean delivery.

KEY WORDS
Apgar score, Cesarean, Norepinephrine, Post spinal hypotension

Citation
INTRODUCTION

Spinal anesthesia is the choice of technique commonly used in today’s world for cesarean section. However, hypotension is the common complication that occurs with spinal anesthesia. The prolonged hypotension generally leads to diminish in uteroplacental blood flow and fetal acidosis. In today’s practice the most commonly and appropriate used vasopressor is phenylephrine in cesarean section. But, use of phenylephrine may cause severe bradycardia and decrease in cardiac output. On the other hand, the use of ephedrine leads to maternal tachycardia, increase incidence of maternal nausea and vomiting and alterations in fetal pH. There are some recent studies which showed that the Norepinephrine leading to increase in heart rate and cardiac output due to mild and dose dependent B-adrenergic effects to counteract the vasoconstriction properties and therefore maintaining the blood pressure and heart rate during spinal anesthesia for cesarean section. Moreover, these recent studies have shown that norepinephrine could be an alternative to phenylephrine in terms of maintaining the blood pressure and heart rate for cesarean section with spinal anesthesia. But different studies done recently does not show the optimal dose of infusion of norepinephrine. So, the main objective of this study is to find out the appropriate dose of infusion of norepinephrine with two different regimens for preventing hypotension during cesarean section following spinal anesthesia.

METHODOLOGY

A prospective, randomized, controlled double blind study was planned. It was conducted on 100 parturient. Approval of this study was obtained from Nobel Medical College Teaching Hospital ethical committee and informed consent was obtained from the recruited mother for the procedure. The study was conducted from November 2021 to October 2022 at Nobel Medical College Teaching Hospital, Biratnagar, Nepal. The randomization was done by computer generated online random number generator. The codes of the patient were kept as a sequential numbered sealed envelope by the anesthesiologist who was not responsible for patient management in this study. The anesthesia junior resident who was not involved in the study was assigned for opening the envelope and preparing the drug as written in each envelope.

The inclusion criteria for this study includes age group of 17 years to 40 years planned for elective cesarean, singleton, full term pregnancy, ASA I and ASA II. The exclusion criteria for this study include Patient with medical co-morbidities (Diabetes Mellitus, CVS disease, severe anaemia, pre-eclampsia and eclampsia and coagulopathy), baseline systolic blood pressure (SBP) less than 100 mmHg, emergency cesarean section, body mass index above 30, systolic blood pressure (SBP) less than 100 mmHg, mean arterial pressure (MAP) less than 60 mmHg, heart rate (HR) less than 60 or more than 100 beats per minute, maternal age more than 40 years, maternal weight more than 100 kg, presence of maternal comorbidities (Diabetes Mellitus, CVS disease, severe anaemia, pre-eclampsia and eclampsia), body mass index below 18.5 kg/m², presence of fetal anomalies, presence of occult bleeding in second trimester, high risk pregnancies, maternal age below 17 years or above 40 years, and maternal weight below 40 kg or above 100 kg.

Routine pre anesthetic check (PAC) was done on day prior to surgery as for elective cases. All patients received of inj. Metoclopramide 10mg and inj. Ranitidine 50mg two hours prior to operation intravenously as per protocol lay down by department of Anesthesiology of our institution. In the preparation room/operation room:

- Baseline non invasive systolic, diastolic, mean arterial pressure was recorded
- Heart rate was recorded
- Peripheral oxygen saturation was recorded
- Continuous ECG recording
- Placement of 18G cannula and IV drip with Ringer Lactate.

With the patient in sitting position, a 25-Gauge Quincke needle was inserted at L3-4 or L4-5 interspinous space and 0.5% heavy bupivacaine 2.2ml was injected intrathecally after ascertaining the free flow of cerebrospinal fluid (CSF). After the subarachnoid block patients were divided in 2 groups;

1. Group 1: 0.025ug/kg/min received 5 ug norepinephrine bolus followed by norepinephrine infusion in a starting dose of 0.025 ug/kg/min.
2. Group 2: 0.050ug/kg/min received 5 ug norepinephrine bolus followed by norepinephrine infusion in a starting dose of 0.050 ug/kg/min.

The bolus dose of norepinephrine was given soon after subarachnoid block was achieved. The norepinephrine infusion was continued 5 minutes after the delivery of fetus and stopped subsequently.

The patients were kept in supine position with left uterine displacement after spinal anesthesia. Non invasive blood pressure (NIBP), Mean arterial pressure (MAP), Heart rate (HR), Pulse oximetry (SPO2) were recorded as baseline. Systolic blood pressure (SBP) and mean arterial pressure (MAP) were recorded at every one-minute interval for 6 readings and then every 2.5 minutes for next 4 readings and then at 5 minutes interval till 5 minutes after delivery of the fetus. Heart rate (HR) was recorded as baseline and in every 2.5 minutes interval. Level of blocks was checked by cotton swab soaked in spirit and surgery was allowed once the level extended up to T6-T8. Patient in whom hypotension developed was treated by IV bolus doses of inj. ephedrine 3mg. If maternal Bradycardia, it was managed with injection Atropine 0.6 mg intravenous bolus.

After delivery of fetus injection oxytocin 5 IU was injected as a single bolus dose, followed by 10 IU infusion at the rate of 30 drops per minute. Total blood loss was recorded at the end of surgery. Neonatal condition was assessed by APGAR score 1, 5 and 10 minutes after the delivery.

The primary outcome of this study was to find the frequency of post spinal hypotension. The secondary outcomes included systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate (HR), frequency of intraoperative nausea and vomiting, intraoperative requirements of ephedrine and atropine, Apgar score at 1, 5 and 10 minutes after the delivery.

Statistical analysis: Data were collected and entered in master chart in MS Excel using SPSS 17.0 (statistical package...
for social science). Categorical data were calculated as percentage. Descriptive data were interpreted as mean (SD) and median wherever required. All variable was analyzed using different statistical test (Independent t Test and chi-squared test) as needed, P value <0.05 interpreted as statistically significant.

Sample size
The sample size was taken as 100 patients with 50 in each group with previous study7 and by using the formula:

\[ n = \frac{(2(x+\beta))^2}{S^2} \]

where \( Z_a = 1.96 \) at 95 % confidence level, \( Z_b = 0.84 \) at 80% power

RESULTS
The demographic characteristics of the two groups are reported in Table 1.

Table 1: Demographic characteristics of the study population

<table>
<thead>
<tr>
<th>Parameters</th>
<th>GROUP A (n=50)</th>
<th>GROUP B (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>24.98±3.55</td>
<td>25.58±4.22</td>
<td>0.610</td>
</tr>
<tr>
<td>Weight</td>
<td>63.56±6.78</td>
<td>60.28±5.87</td>
<td>0.011</td>
</tr>
</tbody>
</table>

The values are in mean (±) SD. P-value < 0.05 is considered to be significant.

Table 2: Baseline mean hemodynamic variables

<table>
<thead>
<tr>
<th>Parameters</th>
<th>GROUP A (n=50)</th>
<th>GROUP B (n=50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>119.72±9.10</td>
<td>120.32±8.88</td>
<td>0.739</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.32±7.22</td>
<td>69.80±5.65</td>
<td>0.055</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>88.12±7.01</td>
<td>86.64±6.12</td>
<td>0.264</td>
</tr>
<tr>
<td>HR/min</td>
<td>89.04±14.04</td>
<td>88±9.71</td>
<td>0.66</td>
</tr>
</tbody>
</table>

The values are in means (±) SD. P- value < 0.05 is considered to be significant. SBP= Systolic Blood Pressure, DBP=Diastolic Blood Pressure, MAP= Mean Arterial Pressure, HR=Heart Rate

Table 3: Comparison of SBP between the groups

<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>SBP GROUP A</th>
<th>SBP GROUP B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>122±9.47</td>
<td>127.62±7.71</td>
<td>0.002</td>
</tr>
<tr>
<td>1</td>
<td>118.18±9.43</td>
<td>123.60±7.80</td>
<td>0.002</td>
</tr>
<tr>
<td>2</td>
<td>111.56±9.20</td>
<td>121.96±8.25</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>3</td>
<td>107.86±14.65</td>
<td>121.34±8.76</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>4</td>
<td>108.00±10.59</td>
<td>121.80±8.57</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>5</td>
<td>113.82±8.75</td>
<td>121.80±10.12</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>7.5</td>
<td>115.74±7.26</td>
<td>121.48±9.51</td>
<td>0.001</td>
</tr>
<tr>
<td>10</td>
<td>117.04±8.39</td>
<td>122.08±6.95</td>
<td>0.002</td>
</tr>
<tr>
<td>12.5</td>
<td>115.93±8.30</td>
<td>123.56±6.03</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>15</td>
<td>117.31±7.90</td>
<td>124.41±7.15</td>
<td>0.001</td>
</tr>
<tr>
<td>20</td>
<td>118.12±6.10</td>
<td>124.00±8.13</td>
<td>0.047</td>
</tr>
<tr>
<td>25</td>
<td>119.86±8.07</td>
<td>130.00±7.07</td>
<td>0.236</td>
</tr>
</tbody>
</table>

The values are in means (±) SD. P- values <0.05 is considered to be significant.

Table 4: Hypotensive episodes after SAB

<table>
<thead>
<tr>
<th>Hypotension</th>
<th>GROUP A (n=50)</th>
<th>GROUP B (n=50)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>23 (46%)</td>
<td>6 (12%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Time of occurrence (minutes)</td>
<td>13.26±4.13</td>
<td>15±6.32</td>
<td>0.546</td>
</tr>
<tr>
<td>Minimum SBP (mmHg)</td>
<td>91.61±8.76</td>
<td>90.67±1.21</td>
<td>0.623</td>
</tr>
<tr>
<td>Minimum DBP (mmHg)</td>
<td>44.04±7.65</td>
<td>52.17±4.95</td>
<td>0.008</td>
</tr>
<tr>
<td>Minimum MAP (mmHg)</td>
<td>59.80±5.29</td>
<td>65±3.46</td>
<td>0.015</td>
</tr>
</tbody>
</table>

P-values <0.05 is considered to be significant. SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, MAP=Mean Arterial Pressure

Figure 1: Comparison of mean intraoperative MAP

Figure 2: Comparison of mean intraoperative Heart Rate

The values of mean of HR of each group was plotted in figure 2. The graph shows no significant difference in HR between the two groups.

Figure 3: Incidence of hypotension

The table 8 shows the side effects encountered in both the groups during the study. The overall incidences of the side effects were nausea (14%), vomiting (4%), bradycardia (2%),
tachycardia (4%), and hypertension (2%). Intraoperatively 7 parturient in each group perceived nausea, and 2 parturient in group A and 7 parturient in group B had vomiting. All women who develop nausea and vomiting were treated with IV ondansetron 4mg. In group B (2%) developed bradycardia. All were treated with IV atropine 0.6mg. Tachycardia was seen in 4% in group A and 2% in group B.

### Table 5: Side effect observed in both the groups during the study

<table>
<thead>
<tr>
<th>Side effects</th>
<th>GROUP A (n=50)</th>
<th>GROUP B (n=50)</th>
<th>Total (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>7(14%)</td>
<td>0</td>
<td>7(14%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2(4%)</td>
<td>0</td>
<td>2(4%)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0</td>
<td>1(2%)</td>
<td>1(2%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2(4%)</td>
<td>1(2%)</td>
<td>3(6%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>1(2%)</td>
<td>1(2%)</td>
</tr>
</tbody>
</table>

The values are in frequency and percentage.

### Table 6: Comparison of APGAR score

<table>
<thead>
<tr>
<th>APGAR</th>
<th>GROUP A</th>
<th>GROUP B</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 minute</td>
<td>7.10±.30</td>
<td>7.00±.00</td>
<td>0.022</td>
</tr>
<tr>
<td>5 minute</td>
<td>8.60±.49</td>
<td>8.34±.51</td>
<td>0.012</td>
</tr>
<tr>
<td>10 minute</td>
<td>9.12±.38</td>
<td>8.76±.43</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

The values are in means (±) SD. P-values <0.05 is considered to be significant.

### DISCUSSION

Different studies recommends that aortocaval compression prevents venous return and therefore sympathetic block leads to venous pooling in the lower limbs to synergistically reduce venous return, decreasing cardiac output and causing maternal hypotension. The decrease of systemic vascular resistance secondary to small artery vasodilation with some degree of venous dilatation is main effect of Spinal anesthesia. Thus, in present days Ephedrine, phenylephrine and Norepinephrine are three commonly used vasopressors during cesarean delivery under spinal anesthesia. Therefore, we thought to compare the appropriate dose of Norepinephrine infusion for preventing post spinal hypotension during cesarean section.

In the present study the mean age in Group A and Group B were 24.98±3.55 years and 24.58±4.22 years respectively. Similarly, the mean weight in Group A and Group B were 63.56±6.78 kg and 60.28±5.87 kg respectively. Our study showed both the groups were comparable with regard to age and weight.

We compared two doses of Norepinephrine infusion 0.025ug/kg/min and 0.050ug/kg/min during cesarean delivery, one being lower dose whereas other being an intermediate dose. Similarly, Ahmed M. Hasanin et al compared three doses for norepinephrine infusion during cesarean section 0.025ug/kg/min, 0.05ug/kg/min and 0.75ug/kg/min and suggested 0.05ug/kg/min being the best dose for norepinephrine infusion during cesarean delivery.

Norepinephrine during spinal anesthesia for maintaining blood pressure during cesarean section had been recently reported first by Ngan Kee et al. As cesarean delivery being performed in every hospital and the main challenge is to prevent the post spinal hypotension, therefore there are lots of new guidelines and protocols being added day by day. Ngan Kee et al recently advocated a study where he used Norepinephrine infusion ranged between 1.25ug/min and 5 ug/min and concluded that Norepinephrine group had a lower incidence of hypotension when compared with controlled group. Though our study was limited only to norepinephrine group and didn’t compare with any control group.

In the present study, the systolic blood pressure (SBP) decreased in both groups in 1 and 2 minutes when compared with baseline, but after that SBP was static in group B through- out the operation whereas it was in decreasing traits in group A. Ngan kee et al also showed that using infusion of 5ug/ml of norepinephrine infusion was more effective in maintaining the blood pressure thus decreasing the incidence of hypotension which was similar finding in our study.

In our study, there was no major reduction of heart rate when compared between the two groups. One patient in group B had bradycardia which was treated with injection atropine. Two patients in Group A had tachycardia whereas one patient in group B had tachycardia which settled by its own as it was transient. Similarly, the study done by A.H Hasanin et al found that bradycardia requiring atropine was seen in 4.3% cases in 0.025ug/kg/min group, 3.2% cases in 0.05ug/kg/min group and 7.3% cases in 0.075ug/kg/min.

Though we didn't study 0.075ug/kg/min infusion group, the other two groups finding were 2% cases had bradycardia in 0.05ug/kg/min and none in 0.025ug/kg/min group in our study.

The incidence of hypotension when compared between two groups in our study, it was found that 46% of patient had hypotension in group A whereas only 6% of patient in group B. Ngan kee et al also had a similar finding to our study that infusion of 5ug/ml norepinephrine was effective in decreasing the incidence of hypotension. Another study by Corke et al and Wei et al also reported the incidence of hypotension in 0.050ug/kg/min infusion group but the incidence of hypotension was much higher in their studies.

Nine patients in 0.025ug/kg/min group had Nausea and Vomiting in our study and this may be due to central hypotension seen more in this group.

Apgar score in context to neonatal wellbeing were compared in both the groups. Though APGAR score was higher in group A compared to group B it was statistically not significant except in 10min score.

### CONCLUSION

The infusion of 0.050ug/kg/min norepinephrine effectively reduced the episode of post spinal hypotension when compared with infusion of 0.025ug/kg/min during cesarean delivery.
LIMITATIONS OF THE STUDY

Further studies may be needed as number of patients in our study were less. The possible bias might arise as norepinephrine were manually prepared; it would be better if computer control infusion were made. The study would be stronger if compared with more norepinephrine infusion doses, as we only compared the two doses of norepinephrine.

ACKNOWLEDGEMENTS

We would like to Sincerely thanks to all my patients, my residents, obstetrics team, colleagues who assisted to make this study possible.

CONFLICT OF INTEREST

There is no conflict of interest to declare.

FINANCIAL DISCLOSURE

None

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