Comparison of effects of norepinephrine and phenylephrine on maternal haemodynamics and foetal well-being after subarachnoid block for elective caesarean sections: A randomised double-blind controlled trial

Dr. Kamabathula Sailaja, Dr. Gita Nath, Dr. Gauri Bule and Dr. Manasa N

DOI: https://doi.org/10.33545/26648849.2024.v6.1a.36

Abstract

Background: Hypotension and decreased cardiac output after subarachnoid block for caesarean delivery result in adverse effects on the parturient and foetus. Though phenylephrine is currently the preferred vasopressor for post-spinal hypotension, norepinephrine may be a more suitable choice because of less negative effects on heart rate and cardiac output. The present study compares the effectiveness of these agents, as prophylactic infusions and therapeutic bolus administration, in managing post-spinal hypotension.

Methods: Hundred parturients scheduled for elective caesarean section under SAB were randomised into the following 4 groups: NE-I and PE-I (norepinephrine and phenylephrine infusions at 2 mcg/min and 25 mcg/min respectively), NE-B and PE-B (norepinephrine and phenylephrine boluses of 8 mcg and 100 mcg respectively). Blood pressure and heart rate were noted every 2 minutes and APGAR noted at 1 and 5 min.

Result: The mean heart rate and systolic blood pressure at each time point did not show any significant differences between groups. Incidence of hypotension was significantly lower in the infusion groups. There was a highly significant difference in the proportion of patients who received vasopressor boluses. Nausea and/or vomiting was significantly more frequent in the bolus groups. There was no significant difference in the 1-minute and 5-minute APGAR scores.

Conclusion: The study shows that both drugs given as prophylactic infusions were more effective at maintaining the blood pressure. The incidence of nausea and vomiting was also significantly lower in the infusion groups. There was no significant difference in effectiveness between the two drugs.

Keywords: Caesarean delivery, spinal hypotension, phenylephrine, norepinephrine

Introduction

Subarachnoid block is the preferred anaesthesia technique for caesarean sections due to its rapid onset and reliable effect. It also avoids airway manipulation and multiple drug administration. However, it is associated with adverse effects, out of which hypotension is an important one. Hypotension is due to the sympathetic block and is accentuated in pregnancy due to physiological changes like aortocaval compression and decreased systemic vascular resistance. The incidence of hypotension is about 70 to 80% [1], and when left untreated, results in adverse effects on the parturient and foetus. Hypotension and decreased cardiac output result in nausea, vomiting, dizziness, and decreased level of consciousness in the parturient. The decreased uteroplacental blood flow results in foetal distress and acidosis. Many methods to reduce hypotension, such as left lateral tilt, application of leg compressors, and preloading and co-loading of crystalloid fluids, have been tried but are not completely effective [2]. Vasopressors have been found to be effective in the prevention as well as treatment of hypotension [3].

Commonly available vasopressors include ephedrine, phenylephrine, mephentermine, noradrenaline, and adrenaline. Ephedrine affects adrenergic receptors (α, β1, β2) directly as well as indirectly, resulting in a slow onset and prolonged action. Phenylephrine acts directly
on α receptors, with a rapid onset and intermediate duration of action. Its use is often associated with a reflex decrease in heart rate and cardiac output \[^4\]. Mephentermine is a mixed α and β adrenergic receptor agonist, with direct and indirect effects, resulting in immediate onset and prolonged action \[^5\]. Noradrenaline is a potent α1 agonist and moderate β1 agonist, with immediate onset and a short duration of action. Adrenaline has an affinity to α1, β1, and β2 receptors with predominant β effects at lower doses and, α effects at higher doses \[^6\].

Phenylephrine is currently the preferred vasopressor for post-spinal hypotension in many parts of the world. However, noradrenaline, with its β agonist action, may be a more suitable option for maintaining maternal blood pressure with less negative effects on heart rate and cardiac output. Apart from the choice of vasopressor, there is some uncertainty as to whether an infusion or bolus dose regime is more effective at preventing post-spinal hypotension. The present study is designed to compare the effectiveness of phenylephrine and noradrenaline, as prophylactic infusions and therapeutic bolus administration, in preventing and treating hypotension in patients under spinal anaesthesia for elective caesarean section. The secondary outcome was their effect on fetal well-being. Based on the comparative dose-response analysis by Ngan Kee, equipotent doses of noradrenaline and phenylephrine were taken as 8 mcg and 100 mcg, respectively \[^7\].

Materials and Methods and Study design

This is a prospective double-blind, randomised, controlled study conducted in Rainbow Children’s Hospital from over a 2-year period. Sample size calculated based on a previous study comparing the effects of bolus administration of phenylephrine and norepinephrine, showed that a total of 98 participants were required \[^8\]. We rounded this off to 100 participants and divided them into 4 groups of 25 each. After approval from the institutional ethical committee, registration with Clinical Trials Registry-India (CTRI/2020/02/023456) and written informed consent, 100 parturients scheduled for elective caesarean section under SAB were recruited for the study over a period between 2020-2022. They were all ASA PS II, aged 18 to 50 years, with a singleton pregnancy. Patients with hypertensive disorders of pregnancy, placental abnormalities like placenta accreta, central placenta previa, anticipated massive blood loss, foetal abnormalities and a history of allergy or hypersensitivity to phenylephrine or norepinephrine were excluded from the study. The subjects were randomly divided into the following 4 groups with the aid of a computer-generated table.

- **Group NE-I**: Norepinephrine 2 µg/min prophylactic infusion for 30 mins (60 µg in 100 ml normal saline over 30 min) and noradrenaline 8 µg bolus for hypotension
- **Group PE-I**: Phenylephrine prophylactic infusion of 25 µg/min for 30 mins (750 µg in 100 ml normal saline over 30 min) and phenylephrine 100 µg bolus for hypotension
- **Group NE-B**: Normal saline infusion (100 ml over 30 min) and noradrenaline 8 µg bolus for hypotension
- **Group PE-B**: Normal saline infusion (100 ml over 30 min) and phenylephrine 100 µg bolus for hypotension.

In order to maintain blinding, the vasopressor infusion and bolus syringe were prepared by an anaesthetist who was not involved in the management of the case or an anaesthesia technician.

After obtaining informed consents for anaesthesia as well as for the study, an 18-gauge intravenous cannula was secured. Standard monitoring including non-invasive arterial pressure, electrocardiography and pulse oximetry were established, and baseline vitals were noted. The patient was then co-loaded with 500 ml of Ringer lactate solution. Using standard sterile technique, a subarachnoid block (at L3-L4 or L4-L5 level) with 2 ml of 0.5% hyperbaric bupivacaine plus 0.5 mL (25 µg) fentanyl was given using 25-G Whitacre needle in the sitting position. The patient was made supine with a left lateral tilt of the table. The highest level of sensory blockade was assessed with ice cubes 5 and 10 minutes after intrathecal injection.

Hypotension was defined as a decrease of systolic blood pressure (SBP) by >20% or SBP< 80 mmHg (whichever is the lowest). The anaesthetist posted in the theatre used the code-labelled syringe to treat hypotension and collected the data for analysis. The patient and the investigator were blinded to the vasopressor used. Blood pressure and heart rate (HR) were noted every 2 minutes till 20 min after the spinal, and every 5 minutes thereafter. After delivery of the baby, a bolus of 3 IU of oxytocin was given over 30 seconds, and an infusion of 3 IU oxytocin per hour was started.

The primary outcome was comparison of maternal SBP and HR, secondary outcome was comparison of incidence of nausea and/or vomiting and Apgar scores at 1 and 5 minutes. The following data were recorded: incidences of hypotension, bradycardia, tachycardia and hypertension; total dose of vasopressor, number of boluses given and intravenous fluid infused intraoperatively. Bradycardia, defined as a HR less than 50 beats/min (bpm), was treated with intravenous atropine 0.6 mg. Tachycardia was defined as HR >120 bpm, and hypertension as a 20% increase in systolic blood pressure from baseline. A paediatrician blinded to the vasopressor used noted the Apgar score at 1- and 5-min. The time intervals from skin incision to baby delivery, uterine incision to baby delivery, spinal anaesthesia administration to baby delivery and skin incision to end of surgery were all noted. Occurrence of dizziness, nausea or vomiting due to maternal hypotension were also noted.

Results

There were no significant differences between the groups as regards age, weight, height and BMI (Table 1), and thus the 4 groups were comparable. ANOVA test was used for comparison of the demographics as well as comparison of HR and SBP at each time point between the 4 groups. Incidences of hypotension, nausea and/or vomiting and need for vasopressor boluses between the groups were compared using the Chi square test, with Yates correction where applicable.

The mean HR and SBP at each time point were compared between groups and did not show any significant difference (Figures 1 and 2). However, the incidence of hypotension, as shown in Table 2, was significantly lower in the infusion groups, NE-I and PE-I, compared to the bolus groups. There was a highly significant difference in the proportion of patients who received vasopressor boluses (Figure 3). Nausea and/or vomiting was significantly more frequent in
the bolus groups compared to the infusion groups, NE-I and PE-I. Hypertension, defined as a 20% increase over baseline systolic blood pressure, was not seen in any patient. Two patients in the infusion groups had transient asymptomatic bradycardia of 50 and 47 beats per minute, respectively, which did not need treatment. There was no significant difference in the 1-minute and 5-minute APGAR scores between the 4 groups (Table 4). The majority (97%) of 1-minute APGAR scores were 8 or more, and only 3 babies had a 1-minute APGAR score of 7 (Figure 4).

Discussion

This study compares treatment with bolus doses of norepinephrine and phenylephrine with prophylactic fixed-dose infusions of both drugs: A 4-way comparison. To our knowledge, this has not been compared previously. The results show that both drugs given as prophylactic infusions were more effective at maintaining the blood pressure, since the incidence of hypotension was lower in both infusion groups compared to the bolus groups. The incidence of nausea and vomiting was also significantly lower in the infusion groups. There was no significant difference in effectiveness between the two drugs. The PE groups needed more rescue vasopressor boluses compared to the respective NE groups, but this did not reach statistical significance.

Traditionally, ephedrine has been the preferred vasopressor to treat post-spinal hypotension based on studies on a sheep model showing that it was best at preserving uterine blood flow [9, 10]. However, with the recognition in the early 2000’s, that ephedrine causes foetal acidosis [11], opinion shifted towards α-agonists like phenylephrine as the first choice in this situation [12], though it has the disadvantage of causing reflex bradycardia and decreased cardiac output. More recently, norepinephrine has been introduced into obstetric anaesthesia practice by Ngan Kee, who demonstrated that the cardiac output and heart rate were better maintained by norepinephrine than phenylephrine [13].

There have been several comparisons between different vasopressors and modes of administration, as summarized in Table 5. Studies comparing bolus administration of norepinephrine with phenylephrine for post-spinal hypotension have found that norepinephrine groups required fewer rescue boluses and had a lower incidence of bradycardia [14, 15]. Prophylactic infusions of both phenylephrine (60-100 μg/min) and norepinephrine (5-15 μg/kg/h) have been demonstrated to be effective at decreasing the incidence of hypotension [16, 18]. Regarding the mode of administration, prophylactic infusions perform better compared to bolus injections in response to hypotension [19, 21]. Ngan Kee compared NE with PE using computer-controlled infusions and demonstrated a higher cardiac output and heart rate with NE, but there were no clinical differences [4]. Comparison of these two agents using fixed rate infusions found that the PE group had more episodes of emesis and needed more rescue boluses [22].

The results of the present study are consistent with previous comparisons of infusion mode vs. bolus administration in that the infusion modes performed better. We did not find a significant difference between the two drugs as regards incidence of hypotension, number of rescue boluses or nausea/vomiting. There was no difference in the foetal well-being as assessed by APGAR scores at 1 minute and 5 minutes. Umbilical cord blood gases were not performed unless there was a clinical indication, to avoid increasing costs for the patient.

There is some controversy regarding administration of norepinephrine via a peripheral cannula, due to the fear of extravasation and possible tissue necrosis. In a retrospective observational study of 14,385 patients who received peripheral NE infusions (20 μg/ml), there were 5 extravasations and no patient had any complication related to this [23]. The concentration used in the present study was 0.6 μg/ml, the infusion was for a limited duration, and the site of infusion was continually observed, thus further reducing the risk of tissue necrosis. There were no adverse effects related to extravasation in our study.

One limitation of this study is that only APGAR scores were used to compare foetal well-being due to ethical concerns regarding the extra cost to the patient. However, the majority of studies on this topic did not find any differences in umbilical cord blood gases as long as the blood pressure is maintained. Transient hypotension of <2 minutes duration does not have adverse effects on the foetus [24]. In the present study, any hypotension was detected and treated promptly with close monitoring and rescue vasopressor boluses.

To avoid bias, we did not include non-elective caesarean sections, high-risk pregnancies, intrauterine growth retardation, placental insufficiency, and pre-eclampsia. Hence, these findings may not be applicable to these populations and further studies are warranted to help select an appropriate vasopressor in these situations.

Table 1: Comparison of age, weight, height and BMI between the 4 groups

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>30.6 (4.0)</td>
<td>30.7 (2.9)</td>
<td>30.4 (4.2)</td>
<td>30.4 (3.2)</td>
<td>0.98</td>
<td>NS</td>
</tr>
<tr>
<td>Weight</td>
<td>78.3 (10.9)</td>
<td>78.9 (12.2)</td>
<td>83.1 (11.2)</td>
<td>85.5 (15.6)</td>
<td>0.14</td>
<td>NS</td>
</tr>
<tr>
<td>Height</td>
<td>157.3 (6.6)</td>
<td>156.5 (4.2)</td>
<td>157.3 (4.8)</td>
<td>161.9 (4.4)</td>
<td>0.98</td>
<td>NS</td>
</tr>
<tr>
<td>BMI</td>
<td>31.7 (4.4)</td>
<td>32.3 (4.9)</td>
<td>33.7 (4.3)</td>
<td>32.6 (5.7)</td>
<td>0.51</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS: not significant, S: significant, HS: highly significant

Table 2: Incidence (%) of Hypotension and Receipt of Vasopressor Bolus

<table>
<thead>
<tr>
<th>Group NE-I</th>
<th>Group PE-I</th>
<th>Group NE-B</th>
<th>Group PE-B</th>
<th>Chi square</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>5 (20)</td>
<td>4 (16)</td>
<td>12 (48)</td>
<td>12 (48)</td>
<td>10.267</td>
<td>0.0164</td>
</tr>
<tr>
<td>Received vasopressor bolus</td>
<td>7 (28)</td>
<td>10 (40)</td>
<td>15 (60)</td>
<td>21 (84)</td>
<td>18.105</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

~ 8 ~
Table 3: Incidence (%) of side effects

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Group NE-I</th>
<th>Group PE-I</th>
<th>Group NE-B</th>
<th>Group PE-B</th>
<th>Chi square</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>0</td>
<td>3 (12)</td>
<td>5 (20)</td>
<td>6 (12)</td>
<td>5.316</td>
<td>0.021</td>
<td>S</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.360</td>
<td>0.782</td>
<td>NS</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2.041</td>
<td>0.564</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4: APGAR scores (Mean, percent in parentheses) in the 4 groups

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Group NE-I</th>
<th>Group PE-I</th>
<th>Group NE-B</th>
<th>Group PE-B</th>
<th>F</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>APGAR 1 min</td>
<td>8.64 (0.57)</td>
<td>8.48 (0.58)</td>
<td>8.6 (0.57)</td>
<td>8.6 (0.58)</td>
<td>0.360</td>
<td>0.782</td>
<td>NS</td>
</tr>
<tr>
<td>APGAR 5 min</td>
<td>9.32 (0.48)</td>
<td>9.12 (0.44)</td>
<td>9.12 (0.33)</td>
<td>9.24 (0.44)</td>
<td>1.350</td>
<td>0.263</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 5: Studies Comparing Phenylephrine and Norepinephrine

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Mode of administration</th>
<th>Comparison</th>
<th>Findings</th>
<th>Foetus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sharkey 2019 [14]</td>
<td>PE, NE</td>
<td>Bolus</td>
<td>PE vs. NE boluses</td>
<td>Fewer rescue boluses in NE group, lower incidence of bradycardia</td>
<td>No difference in foetal BG and APGAR</td>
</tr>
<tr>
<td>Puthenveettil 2019 [15]</td>
<td>PE, NE</td>
<td>Bolus</td>
<td>PE vs. NE boluses</td>
<td>Fewer rescue boluses in NE group</td>
<td>No difference in foetal BG and APGAR</td>
</tr>
<tr>
<td>Ngan Kee 2004 [16]</td>
<td>PE, NE</td>
<td>Prophylactic infusion 100 µg/min</td>
<td>Infusion vs. control</td>
<td>PE infusion safe and effective</td>
<td>No difference in foetal BG and APGAR</td>
</tr>
<tr>
<td>Muzaffar 2016 [18]</td>
<td>PE</td>
<td>Prophylactic infusion 100, 80 and 60 µg/min</td>
<td>PE infusion rates</td>
<td>All doses effective but high incidence of hypertension and bradycardia</td>
<td>No difference in foetal BG</td>
</tr>
<tr>
<td>Chen 2018 [17]</td>
<td>NE</td>
<td>Prophylactic infusions 5, 10, 15 µg/kg/h</td>
<td>NE infusion rates</td>
<td>5 and 10 µg/kg/hr reduced hypotension without adverse effects</td>
<td>No difference in foetal BG</td>
</tr>
<tr>
<td>Ngan Kee 2018 [19]</td>
<td>NE</td>
<td>Infusion (2.5 µg/min) vs. boluses of 5 mcg</td>
<td>NE infusion vs. boluses</td>
<td>Infusion maintained BP closer to baseline</td>
<td>No difference in foetal BG and APGAR</td>
</tr>
<tr>
<td>Magawa 2022 [20]</td>
<td>PE</td>
<td>Retrospective study 220 patients</td>
<td>Prophylactic PE (0.3 µg/kg/min) vs. boluses of PE or ephedrine</td>
<td>PE infusion vs. boluses More hypotension in bolus group</td>
<td>Lower pO2 and APGAR scores in bolus group</td>
</tr>
<tr>
<td>Siddik-Sayyid 2014 [21]</td>
<td>PE</td>
<td>PE infusion (0.75 µg/kg/min) vs. PE boluses 100 µg</td>
<td>PE infusion vs. boluses</td>
<td>Lower incidence of hypotension and nausea/vomiting in infusion group</td>
<td>No difference in foetal BG</td>
</tr>
<tr>
<td>Ngan Kee 2015 [14]</td>
<td>PE, NE</td>
<td>Computer controlled NE vs. PE infusions</td>
<td>NE vs. PE infusions</td>
<td>Both effective for maintaining blood pressure Higher cardiac output in NE group 5 min after spinal</td>
<td>No difference in foetal BG and APGAR</td>
</tr>
<tr>
<td>Vallejo 2017 [22]</td>
<td>PE, NE</td>
<td>Prophylactic infusions NE (0.1 µg/kg/min) vs. PE (0.05 µg/kg/min)</td>
<td>PE vs. PE infusions</td>
<td>PE group needed more boluses and had more emesis</td>
<td>No difference in and APGAR</td>
</tr>
<tr>
<td>Present study</td>
<td>PE, NE</td>
<td>Prophylactic infusions - NE (2 µg/min) and PE (25 µg/min) Rescue boluses - NE 8 and PE 100 µg</td>
<td>4-way comparison</td>
<td>Both infusions more effective than boluses</td>
<td>No difference in foetal well-being</td>
</tr>
</tbody>
</table>

Fig 1: Comparison of Heart Rate
Fig 2: Comparison of Systolic Blood Pressure

Fig 3: Incidence of Hypotension, Vasopressor Administration, Nausea & Vomiting (N&V)

Fig 4: APGAR scores at 1 minute. Yates Chi square 1.817, Yates’ p value 0.9, NS
Fig 5: APGAR Scores at 5 min. Yates Chi square 3.077, Yates’ p value 0

Conclusion
In our study, both phenylephrine and noradrenaline infusions were more effective than bolus administration at preventing hypotension after spinal anaesthesia for caesarean section. There was no statistically significant difference between the two agents, but noradrenaline seemed marginally better. There was no difference in the APGAR scores between the four groups.

Conflict of Interest
Not available.

Financial Support
Not available.

References
13. Ngan Kee WD, Lee SW, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anaesthesia for cesarean delivery. Anesthesiology. 2015;122(4):736-745. DOI: 10.1097/ALN.0000000000006061


How to Cite This Article