Effectiveness of Intravenous Prophylactic Phenylephrine for the Prevention of Spinal Anaesthesia Induced Hypotension during Caesarean Section. A Prospective Observational Study

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Abstract

**Background:** Hypotension is one of the common complications of spinal anaesthesia. It has many detrimental effects to the mother and fetus if left untreated. Recently, phenylephrine is introduced for the treatment of hypotension in our hospital. However, its efficacy on the prevention of spinal anaesthesia induced hypotension is still under controversy. We aimed to assess the effectiveness of phenylephrine prophylaxis on spinal hypotension after caesarean section.

**Methods:** A prospective observational study was conducted at the University of Gondar Hospital. Patients were allocated based on treatment received; 50/100 µgm phenylephrine prophylaxis vs. no prophylaxis. PR, SBP, DBP, SPO2 and APGAR score were measured before, immediately after spinal anaesthesia, every 2 min intra operatively till the delivery of the baby and every 5 min after delivery for 20 min, and every 10 min for 1 h in postoperative period.

**Results:** The incidence of hypotension was significantly lower for those participants with prophylactic phenylephrine (26% vs. 81.6%, p<0.001) compared to the non-treatment group. Systolic and diastolic blood pressures immediately after spinal anaesthesia till delivery and after delivery of the baby were significantly lower in the none treatment group at all times (p<0.05). Moreover, the number of rescue treatments and total amount of fluid given during the intraoperative period for the treatment of hypotension were more in the non-treatment group (P=0.001). The APGAR scores at 1 and 5 min and postoperative vital signs were comparable between groups.

**Conclusion and recommendation:** The incidence of spinal anaesthesia induced hypotension was high. Prophylactic intravenous phenylephrine bolus remarkably reduced the incidence of spinal induced hypotension compared to the non-treatment group. We recommend prophylactic phenylephrine for parturients undergoing caesarean section under spinal anaesthesia. Moreover, other pharmacological and non-pharmacological methods need to be considered as the incidence of hypotension is still high in the treatment group.

Keywords: Caesarean section; Spinal anesthesia; Hypotension; Apgar score; Phenylephrine Prophylaxis; Effectiveness

Introduction

Spinal anaesthesia is a widely used anaesthetic technique for caesarean as it avoids the risks of general anesthesia related to difficult intubation and aspiration of gastric contents [1-3]. Spinal anaesthesia in pregnant women is associated with greater incidence of hypotension (80%) observed in non-pregnant women despite the preloaded or coloaded fluid [4].

Post spinal hypotension remains common despite several measures used to reduce both incidence and severity [5,6] of subarachnoid block and it is decrement of systemic blood pressure due to systemic vasodilation secondary to sympathetic blockade by intrathecal administration of local anesthetics. Hypotension can be defined as reduction of blood pressure by 20% from base line or systolic blood pressure <90 mmHg [7-9]. A reduction in systemic vascular resistance as a consequence of sympathetic blockade, extensive neural blockade because of a contracted subarachnoid space, higher level of sympathetic block and aorthocaval compression by gravid uterus, as well as to the already low decreased systemic vascular resistance associated with pregnancy [10,11].

The effect of spinal anesthesia on fetal heart rate is due to maternal hypotension and subsequent fetal hypoxia. Maternal hypotension of 80 mmHg for five min almost always results in hypoxic fetal bradycardia [12,13]. The severity of post spinal hypotension will be more aggravated and ended up with many detrimental clinical effects [14-18]. Various pharmacologic and non pharmacologic [][19,20] methods have been used to prevent, treat and decrease adverse effects of post spinal anaesthesia hypotension [20-22]. However, non-pharmacologic mechanisms are associated with high incidence of high spinal block and unilateral block especially when hyperbaric local anaesthetics are used [23]. As pharmacologic methods, are associated with hemodynamic instability (refractive hypertension, bradycardia, and tachycardia) and fetal acid base disturbance and uterine vasoconstriction [24-26], other modalities such as fluid
administration, left lateral position and Trendelenburg positions should be considered [27,28].

Many studies are conducted to determine effective drugs to prevent and control hypotension such as ephedrine, phenylephrine, adrenaline, metaraminol, and dopamine [29-35]. However, there is no known gold standard drug for prevention and control of post spinal hypotension. Furthermore, Cochrane review of 75 trials (4,624 women) different hypotension prevention methods showed that crystalloids were less effective than colloids but more effective than no fluid in preventing hypotension following spinal anaesthesia at caesarean section. Ephedrine and phenylephrine when given individually were more effective than crystalloids or controls in preventing hypotension but no significant differences in hypotension were seen between ephedrine and phenylephrine [36].

Although, non-pharmacologic methods are alternatives, hypotension during spinal anaesthesia common and almost all parturients required vasopressor for intervention [37]. Phenylephrine is a selective α1-adrenergic receptor agonist which has been used to increase blood pressure. Because of its sympathomimetic effect without beta-adrenergic activity, it does not increase contractility force and output of cardiac muscle; it may increase BP resulting in a slow heart rate through stimulation of vascular baroreceptors as reflex bradycardia is side effect of its IV administration [38,39]. Phenylephrine used as alternative vasopressor for treatment and prevention of post spinal hypotension. Some studies showed different results to choose the best drug during cesarean delivery under spinal anesthesia but associated with some side effects such as hypertension and bradycardia [40].

Recently, phenylephrine is introduced in our hospital to treat spinal anaesthesia induced hypotension using different dose regimens (50 µgm, 100 µgm). However, its efficacy on the prevention of spinal anaesthesia induced hypotension remains unexplored in our hospital. We aimed to assess the effectiveness of prophylactic intravenous phenylephrine bolus on the prevention of spinal anaesthesia induced hypotension in parturients undergoing caesarean section.

Methods

Institutional based prospective observational study was conducted in University of Gondar Hospital from May 1-30, 2017. The University of Gondar Hospital is one of the largest referral and teaching hospitals in the Amhara region and serving around 5 million people. Post-spinal hypotension is being routinely managed by vasoconstrictors (phenylephrine, adrenaline) as prophylaxis or treatment by anaesthetists during operation.

Study population

All mothers who gave birth by caesarean section in University of Gondar Hospital during the study period.

Inclusion and exclusion criteria

All ASA II and ASA III parturients who underwent cesarean section under spinal anaesthesia (parturients who took phenylephrine prophylaxis or who didn’t take any prophylactic vasoconstrictor). Patient refusal, massive obstetric hemorrhage, complicated surgery (such as hysterectomy), myocardial infarction of <3 months, parturients who have allergic history for phenylephrine, failed spinal or total spinal converted to general anesthesia were excluded from the study.

Variables of the study

Dependent variable

The incidence of hypotension, maternal hemodynamic change (HR and BP) at different time intervals in the intraoperative and postoperative period (0-1 h), Apgar score at 1 and 5th min were compared among participants with and without prophylactic phenylephrine.

Independent variables

Socio-demographic variables (age, weight, height) indication for caesarian section, parity, gestational age, duration of surgery, time from skin incision to delivery of fetus, ASA category, the amount of fluid preloaded or coloaded, level of SA block (sensory and motor), type and dose of local anesthetics given.

Operational definitions

Hypotension: Decrease in systolic blood pressure from baseline by 20-25% [41,42].

Post spinal hypotension (PSH): Reduction of systolic blood pressure from baseline by 20% following spinal anaesthesia [43,44].

Bradycardia: Reduction of heart rate to <60 bpm [45].

Tachycardia: Increment of heart rate >100 bpm by whatever the cause [46].

Hypertension: Elevation of blood pressure more than 140/90 mmHg and it could sometimes be resistant for treatment [47].

Nausea and vomiting: Sense of discomfort, hyper salivation or vomiting ingested matter or any content after any surgical or anesthetic intervention [48].

Effectiveness of phenylephrine: It is the ability of the drug to decrease incidence of hypotension and it could be assessed by blood pressure change after it has given.

Safety of phenylephrine: It is assessed by change in heart rate (bradycardia), blood pressure (hypertension) and neonatal outcome (Apgar) score.

Sample size and sampling procedure

All consecutive laboring mothers (prospectively) who delivered by cesarean section under spinal anaesthesia during the study period were included in the study.

Data collection procedures

Ethical approval was obtained from University of Gondar, School of Medicine ethical review board (Ref.No. SOM /1004/4/2017). Written informed consent was obtained from study participants before commencing the study. Recently, phenylephrine is introduced in our hospital for the prevention of spinal anaesthesia induced hypotension with different dose regimens (50 µgm and 100 µgm). Parturients who underwent caesarean section were classified in to three groups: phenylephrine 50 µgm, phenylephrine 100 µgm and none prophylaxis group based on their exposure (treatment by the responsible
Phenylephrine IV bolus was given immediately after spinal anaesthesia (after a patient is positioned). We investigators did not involve in the perioperative management of patients. Pulse rate, non-invasive blood pressure (NIBP), peripheral oxygen saturation (SPO2) were measured before, immediately after spinal anaesthesia, every 2 min intra operatively till delivery of the baby and then every 5 min after delivery for 20 min and every 10 min for 1 h in postoperative period. Anaesthetic management including prophylactic phenylephrine was up to the choice of the responsible anaesthetists. The data collector observed the responsible anaesthetist whether he or she gave vasoconstrictors during administration of spinal anaesthesia. Mothers who took bolus dose of phenylephrine and who were not taking drug were identified by the data collector (Figure 1).

The data collector continuously observed the hemodynamic variables of parturients, intraoperative anaesthetic and surgical interventions, and Apgar score during the study period without having place in intervention in whatever the case. Level of sensory block was assessed and recorded by pinprick after completion of spinal anaesthesia. Motor block was assessed and recorded by Bromage motor scale. Total amount of intraoperative fluid, estimated blood loss, doses of drugs for treatment of hypotension and duration of surgery were recorded by one of the data collector.

### Data analysis

After completion of data collection, the data were checked for errors and coded. The coded data were entered to SPSS version 20.0 statistical package and analysis was performed. Numerical variables were analyzed using independent student t-test and Man-Whitney U test as appropriate. Incidence of hypotension was compared using chi-square test. P value <0.05 was considered statistically significant. Numerical data were presented as mean ± Standard deviation or median (IQR) and categorical data as proportions (%). Baseline characteristics and risk level were checked for similarity in the groups.

### Results

#### Socio-demographic characteristics of study participants

A total of 113 parturients were given spinal anaesthesia. One patient was excluded because spinal anaesthesia failed and converted to general anaesthesia and other two patients are excluded due to missing data. All (110) laboring mothers who underwent caesarean delivery under spinal anaesthesia during the study period were included. The indications for caesarean section were cephalopelvic disproportion 20 (18.2%), non-reassuring fetal heart rate 22 (20%), failed induction 18 (16.4%), previous caesarean section scar 21 (19.1%), malpresentation 17 (14.5%), mild antepartum hemorrhage 5 (4.5%), and others (oligo/ polyhydramnios, PROM) 7 (6.4%).

All patients have been premeditated with 10mg metoclopramide and 200 mg cimetidine. Of these patients, 50 mothers were given prophylactic phenylephrine (37 patients=50 micrograms and 13 patients=100 micrograms) immediately after spinal anaesthesia with 2.5 ml of 0.5% plain bupivacaine and 60 were not given any prophylactic drug. The demographic characteristics (age, height, weight, gestational age) were comparable between the groups (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Prophylactic given (n=50)</th>
<th>Prophylactic not given (n=60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>27.6 ± 3.844</td>
<td>28.13 ± 5.061</td>
<td>0.542</td>
</tr>
<tr>
<td>Weight in kilograms</td>
<td>63.38 ± 10.57</td>
<td>63.58 ± 6.298</td>
<td>0.901</td>
</tr>
<tr>
<td>Height in centimeters</td>
<td>159.96 ± 5.32</td>
<td>158.76 ± 4.42</td>
<td>0.225</td>
</tr>
<tr>
<td>Gestational age in weeks</td>
<td>38.26 ± 1.38</td>
<td>38.23 ± 0.88</td>
<td>0.907</td>
</tr>
<tr>
<td>ASA Class</td>
<td></td>
<td></td>
<td>0.882</td>
</tr>
<tr>
<td>I</td>
<td>34 (30.9%)</td>
<td>40 (36.4%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>16 (14.5%)</td>
<td>20 (18.2%)</td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td>0.431</td>
</tr>
</tbody>
</table>
Table 1: Comparison of socio-demographic variables between groups.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Related to anaesthesia and surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline systolic BP</td>
<td>Prophylaxis given (n=50)</td>
<td>121.34 ± 7.91</td>
</tr>
<tr>
<td></td>
<td>Prophylaxis not given (n=60)</td>
<td>75.28 ± 6.35</td>
</tr>
<tr>
<td></td>
<td>Duration of surgery (min)</td>
<td>91.34 ± 6.07</td>
</tr>
<tr>
<td></td>
<td>Amount of fluid given preoperatively (ml)</td>
<td>97.16 ± 1.67</td>
</tr>
<tr>
<td></td>
<td>Incision starting time to delivery of baby (min)</td>
<td>500 (500)</td>
</tr>
<tr>
<td></td>
<td>Estimated blood loss (ml)</td>
<td>600 (500)</td>
</tr>
<tr>
<td></td>
<td>Duration of surgery (min)</td>
<td>8.5 (4)</td>
</tr>
<tr>
<td></td>
<td>Estimated blood loss (ml)</td>
<td>600 (112.5)</td>
</tr>
<tr>
<td></td>
<td>Duration of surgery (min)</td>
<td>50 (15)</td>
</tr>
</tbody>
</table>

Values are presented as: Mean ± SD, Median (IQR), independent student t-test, Mann Whitney u test and p<0.05 is statistically significant.

Table 2: Comparison of baseline vital signs, factors associated with surgery and anaesthesia between groups.

The incidence of hypotension
The incidence of hypotension between participants who took prophylactic phenylephrine and those who didn't take the drug was different. Of 50 participants who took phenylephrine (50 or 100 microgram) only 13 (26%) had 1 or more episodes of hypotension, whereas of 60 participants who didn't take any prophylactic drug 49 (81.6%) developed hypotension episodes (P<0.001) (Figure 2).
Parameter | Prophylactic given (n=50) | Prophylactic not given (n=60) | p-value
--- | --- | --- | ---
Level of sensory block | | | 0.074
T4-T6 | 13 (11.8%) | 28 (25.4%) | 
T7-T8 | 21 (19.0%) | 20 (18.1%) | 
T9-T10 | 16 (14.5%) | 12 (10.9%) | 
Level of Motor block | | | 0.999
Bromage 2 | 0 (0%) | 1 (0.9%) | 
Bromage 3 | 50 (45.4%) | 59 (53.6%) | 
Incidence of hypotension between prophylactic phenylephrine dose regimens | | | 
Prophylactic dose | 50 µg | 100 µg | P-value
Incidence of hypotension | 13 (35%) | 0 (0%) | 0.013
Treatment of hypotension between groups | | | 
Prophylactic | No prophylactic | 
Dose of drug for treatment of hypotension | 25 µg (25)a | 25 µg (10)a | 0.005
Total amount of fluid (preop+ intraop, ml) | 1500 (100)a | 1500 (300)a | <0.001

Values are presented as: number (%); a=median (IQR), chi-square test and p<0.05 is statistically significant.

Table 3: Comparison of level of block (sensory and motor) between groups, incidence of hypotension between two prophylactic phenylephrine doses.

**Intraoperative vital sign changes overtime and neonatal outcome**

Blood pressure (systolic and diastolic), pulse rate and saturation were observed every 2 min of time interval starting from immediate time after SA till delivery, at delivery and every 5 min after delivery for 20 min. Systolic and diastolic blood pressure immediately after SA till delivery of the baby were significantly lower in those without prophylactic drug (P<0.001) all the time (Table 4). In addition, the blood pressure (systolic and diastolic) was significantly lower during the intraoperative period including the whole time after delivery despite different treatment modalities as it was shown by p-value of less than 0.05. Even though the blood pressure was not expected to be lower at immediate period after SA, it could be due to the autonomic effect of SA anaesthesia which usually starts at this time. However, pulse and were not significantly different throughout intraoperative period between the groups (Table 4).

| Parameter intraoperatively | Systolic blood pressure | Diastolic blood pressure | Heart rate |
| --- | --- | --- | ---
| | Prophylactic given | Prophylactic not given | P-value | Prophylactic given | Prophylactic not given | P-value | Prophylactic given | Prophylactic not given | P-value |
| Immediately after SA | 111.50 ± 17.36 | 89.86 ± 10.99 | 0.001 | 65.02 ± 12.67 | 52.83 ± 9.07 | 0.001 | 99.74 ± 15.55 | 94.71 ± 17.44 | 0.117 |
| 2 min | 110.00 ± 15.75 | 91.83 ± 11.49 | 0.001 | 65.16 ± 12.75 | 56.58 ± 10.22 | 0.001 | 94.52 ± 19.63 | 95.98 ± 15.35 | 0.662 |
| 4 min | 106.46 ± 13.36 | 90.93 ± 11.12 | 0.001 | 64.38 ± 11.76 | 53.18 ± 9.42 | 0.001 | 92.32 ± 14.56 | 94.01 ± 12.85 | 0.518 |
| 6 min | 108.98 ± 15.15 | 91.33 ± 12.51 | 0.001 | 65.48 ± 11.71 | 53.85 ± 10.57 | 0.001 | 92.68 ± 12.83 | 93.38 ± 11.73 | 0.765 |
| 8 min | 107.88 ± 14.68 | 91.38 ± 11.78 | 0.001 | 63.92 ± 11.67 | 53.50 ± 10.19 | 0.001 | 88.44 ± 17.63 | 92.53 ± 12.65 | 0.172 |
Table 4: Comparison of intraoperative SBP, DBP and heart rate before and after delivery.

Neonatal outcome was comparable between groups as it is computed by Apgar score of 1st and 5th min which were not significantly different. However, the overall number of hypotension episodes and number of treatments (rescue) given for hypotension were significantly higher in those who didn’t take prophylactic phenylephrine (Table 5).

Table 5: Comparison of outcome variables related to neonatal outcome, number of hypotension episodes and number of treatments for hypotension.

Postoperative vital sign changes overtime

Vital signs (blood pressure, pulse rate and saturation) were measured and observed starting from immediate postoperative period for 1 h. Systolic blood pressure was significantly different between groups at immediate post-operative period, at 20th min and 30th min (P<0.001). Diastolic blood pressure was significantly lower for those participants with no prophylaxis at most of the times in post-operative period except at immediate pot-operative period till 10th min post-operatively. Whereas pulse rate and saturation were comparable during post-operative period between groups No patient has developed vomiting despite those many episodes of hypotension during intraoperative and post-operative period (Table 6).
phenylephrine group was low (26%) compared with a study conducted by Warwick D et al. that the incidence of hypotension without prophylactic drug was high (88%) whereas 23% in those who received prophylactic phenylephrine (26%).

This study, the incidence of hypotension in prophylactic phenylephrine group was 33% whereas it was 70% in placebo group. In our study, the incidence of hypotension without prophylactic phenylephrine was significantly higher than those with prophylactic phenylephrine and without prophylaxis unlike another study where higher incidence of bradycardia with 100 mg bolus phenylephrine was reported. This discrepancy could be due to the small dose (50 µgm) used in our study for the majority of parturients. Furthermore, it is supported by another systematic review on 7 trials in which the Apgar score at 1st and 5th min was >7 [31,51].

The incidence of hypotension was significantly lower in this study unlike other studies with bolus phenylephrine, could be due to the application of the hypotension definition for earlier times after spinal anaesthesia given in which time the drug is expected to be effective. Even though the prophylaxis controls hypotension at earlier time after administration, there were many hypotension episodes in the intraoperative period which were clinically significant. The number of hypotension episodes intraoperatively differs significantly between groups (P<0.001).

Limitation and Strength of the Study

This is not a randomized control trial study as our university ethical board prohibited RCT by graduate students. Inter-anaesthetist practice variation such as preoperative optimization, intraoperative management including speed of injection of local anaesthetics, level of the block, timing of administration of phenylephrine prophylaxis, the dose of vasoconstrictor drugs etc, could possibly affect the outcome of the study.

This is the first study in our hospital which could enhance the use of prophylactic phenylephrine for the prevention of spinal anaesthesia induced hypotension for parturients undergoing caesarean section.

Conclusion and Recommendation

The incidence of spinal anaesthesia induced hypotension was high. Prophylactic intravenous bolus phenylephrine remarkably reduced the incidence of spinal induced hypotension compared to the non-treatment group. In addition, no parturient developed hypotension among who received 100 µgm phenylephrine. We recommend prophylactic phenylephrine (100 µgm) for parturients undergoing caesarean section under spinal anaesthesia. Moreover, other pharmacological and non-pharmacological methods need to be considered to optimally manage spinal anaesthesia induced hypotension as the incidence of hypotension was still high in.
phenylephrine treated group. Furthermore, we recommend RCT study in this hospital and other similar settings in the country with large cohort of patients.

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References


