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ORIGINAL RESEARCH OBSTETRIC ANESTHESIA

Comparison of prophylactic phenylephrine versus noradrenaline boluses for hemodynamic stability during elective cesarean delivery under spinal anesthesia–an observational study

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Abstract

Background: Profound hypotension and bradycardia following spinal anesthesia (SA) during cesarean delivery (CD) result in catastrophic maternal and fetal consequences. Phenylephrine with its appealing α agonist property proved to be a valid vasopressor for correction of hypotension during SA but with side effects like reflex bradycardia and fall in cardiac output. Noradrenaline is a rational substitute to phenylephrine due to its mild β and prominent α adrenergic properties, but is reserved as an inotrope mainly for medical crisis management. We conducted a comparative observational study of noradrenaline with phenylephrine using bolus doses for preventing hypotension and fetal outcome during CD under SA.

Methodology: Hemodynamic changes and fetal outcomes were studied in 102 pregnant patients undergoing cesarean section out of which 51 patients received a prophylactic bolus dose of phenylephrine100 µg and the rest received Noradrenaline 8 µg immediately after SA and the same bolus dose was repeated to maintain SBP ≥ 90% of the baseline. In this study, we compared the maternal hemodynamic variables, Apgar score, and maternal complications.

Results: Mean heart rate (90.1 vs. 87.3), mean Systolic blood pressure (119.6 vs. 109.2), mean arterial pressures (89.5 vs. 78.6) and mean diastolic pressures (74.6 vs. 67.3) in the noradrenaline group were significantly higher only at one minute of SA ($P < 0.05$), but later part the differences become statistically not significant ($P > 0.05$). Maternal complications such as bradycardia, hypotension, nausea, vomiting and the fetal outcomes were comparable between the groups.

Conclusion: Prophylactic Noradrenaline is equally effective as prophylactic phenylephrine in preventing spinal hypotension with better hemodynamic stability.

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Clinical trial registration number: CTRI/2019/06/026599 (Indian)

Key words: Noradrenaline; Phenylephrine; Cesarean section; Anesthesia, Spinal; Hypotension

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1. Introduction

Neuraxial anesthesia for cesarean delivery (CD) has significantly reduced maternal mortality by avoiding manipulation of the airway, the mother being awake and promoting early bonding of mother and child, effective postoperative analgesia and quicker maternal recovery.[1-2] Hypotension (74%), bradycardia and nausea occur often during spinal anesthesia (SA) for a CD which is further compounded by aortocaval compression.[3] When hypotension is not recognized early, serious maternal cardiovascular collapse, brain stem ischemia, altered sensorium, vomiting with aspiration and even deaths have resulted. Predominantly in patients where there is already a fetal compromise, sustained hypotension may lead to decreased uterine blood flow (60%) and fetal acidosis.[2] For the better outcome of both mother and fetus, hemodynamic stability is of utmost importance during CD under SA.[4-5]

Vasopressors through their effects on α and β adrenergic receptors play a key role in the pharmacological management of hypotension during SA. Ephedrine being a mixed α and β adrenergic agonist produces a dose-related correction of hypotension but with increasing incidence of fetal acidosis.[3] Clinical surveys later supported a predominant α agonist vasopressor like phenylephrine to be a better alternative in terms of correction of hypotension and fetal wellbeing.[6] Phenylephrine has predominantly an α1 effect and is practically devoid of β effects in clinical doses, but produces baroreceptor regulated bradycardia and fall in maternal cardiac output at inadvertent higher doses.[7-8] The neonatal wellbeing was found to be much superior with phenylephrine in the presence of progressing acidaemia.[9]

Noradrenaline a forerunner of epinephrine, efficient than phenylephrine with balancing effects of combined feeble β agonist and stronger α effect with better hemodynamic status and lesser tendency to produce bradycardia, was found to be more attractive in obstetric anesthesia.[10,11]

Prophylactic infusion or bolus administration of vasopressors was found to be more valid than the reactive treatment of hypotension as well as in the prevention of nausea and vomiting during SA for cesarean section.[12] The American Society of Anesthesiologists/Society for Obstetric Anesthesia/Perinatology Task Force made recommendations on the usage of vasopressors for both prophylactic and corrective treatment of hypotension during SA.[5] Although phenylephrine is currently accepted as a popular vasopressor of choice in obstetric anesthesia, we made a study aimed at comparing prophylactic boluses of phenylephrine (100 µg) and norepinephrine (8 µg) on maternal hemodynamic and neonatal outcome following SA in CD.

2. Methodology

The current observational study was conducted over 2 years after approval from the institutional ethics committee and registration with the Clinical Trials Registry of India. Written informed consents were taken from 120 patients enrolled in this study and evaluated one day before surgery. The inclusion criteria were full-term, singleton pregnant women, ASA II, scheduled for elective CD under SA. Patients with obesity, diabetes, cardiac disease, hypertensive disorders of pregnancy, CKD, non-assuring fetal status, peripartum bleeding, age less than 18 years or allergy to drugs used in this study were excluded. In the end 102 parturients were included in the study (Figure 1).

All parturients starving overnight received premedication with oral ranitidine 150mg, metoclopramide 10 mg on the previous night and the day of surgery were shifted in the left lateral position. In the operating room, standard monitors like non-invasive blood pressure (NIBP), pulse oximetry (SpO_2), and electrocardiography were connected and baseline vital parameters were recorded. NIBP and heart rate (HR) were recorded every minute until three consecutive readings with a difference of not more than 10% were achieved and considered as baseline blood pressure and heart rate.

An intravenous cannula (18G) was secured, and a fluid co-load of 20 mL/kg Ringer's Lactate was given, after which the rate of fluid infusion was reduced to 4 mL/kg/h until the delivery of the baby. Subarachnoid block (SAB) was performed in the left lateral position with 2 ml of hyperbaric bupivacaine 0.5% at L2-L3 or L3-L4 intervertebral space, with a 25G Quincke's spinal needle. The patients were immediately turned supine, and a wedge was placed under the right buttock and a block up to T6 was achieved. Blood pressure, heart rate (HR), and oxygen saturation were measured every minute till the

Table 1: Comparative demographic data and surgical times

Parameter	Group	N	Mean ± SD	t	P-value
Age (y)	Noradrenaline	51	28.710 ± 3.336	-1.015	0.313
	Phenylephrine	51	29.390 ± 3.493		
BMI (Kgm^2)	Noradrenaline	51	25.784 ± 3.966	-1.908	0.06
	Phenylephrine	51	27.197 ± 3.499		
Delivery time (min)	Noradrenaline	51	7.59 ± 2.3	0.106	0.916
	Phenylephrine	51	7.59 ± 1.32		
Surgery time (min)	Noradrenaline	51	42.63 ± 5.07	-0.1	0.92
	Phenylephrine	51	42.73 ± 4.82		

Data presented as mean ± SD, df (degrees of freedom); Independent T-test used for comparison of two groups

delivery of the baby and later on every 5 min till the end of the surgery.

The The study population was divided into two groups of 51 each. Group PE included 51 patients who received prophylactic phenylephrine 100 µg bolus. and Group NA received 8 µg noradrenaline as a prophylactic bolus, immediately after turning the parturients supine following SA. The vasopressor drug solutions were prepared in 10 ml syringes; e.g., phenylephrine 100 µg = 2ml, or noradrenaline 8 µg = 2 ml.

We defined hypotension as systolic blood pressure (SBP) < 80% of the baseline; hypertension >120% of the baseline and bradycardia < 60 beats/min. Rescue bolus doses in both the groups with the same designated vasopressor were given, whenever baseline SBP dropped below 80% of the baseline reading. Intravenous atropine 0.6 mg was administered when HR dropped below 50 beats/min.

The primary outcome was to compare the incidence of hypotension between the groups. Secondary outcome parameters noted were the incidence of bradycardia, tachycardia, hypertension, and nausea / vomiting in the mother, the total dose of vasopressor used till the delivery of the baby, and the APGAR scores of the neonate at 1st and 5th minutes. The data was collected and analysed.

The calculation of sample size was based on an earlier study by Sharhey AM et al. (2019)[13], published in "Anesthesia and Analgesia" with the two ratios for bradycardia of 10.7% and 37.5% using formula for calculating the sample size of two propotions, at alpha error of 5%, power of 80 % we needed a minimum sample size of 40 in each group.

Data analysis was done by using independent t test for comparison of the two groups in terms of the hemodynamics, heart rate, age, height. chi-square test for normal deviation of data and $P < 0.05$ was considered significant. SPSS version 25.0 was used to conduct the analysis.

3. Results

One hundred and thirty two patients posted for elective CD under SA were assessed initially and the data was collected from 120 patients to compensate for data loss and finaly 102 patient data was analysed as given in flowchart below (Figure 1). Demographic data and surgical times required were comparable in both groups (Table 1). Figure 2 shows the mean baseline HR and

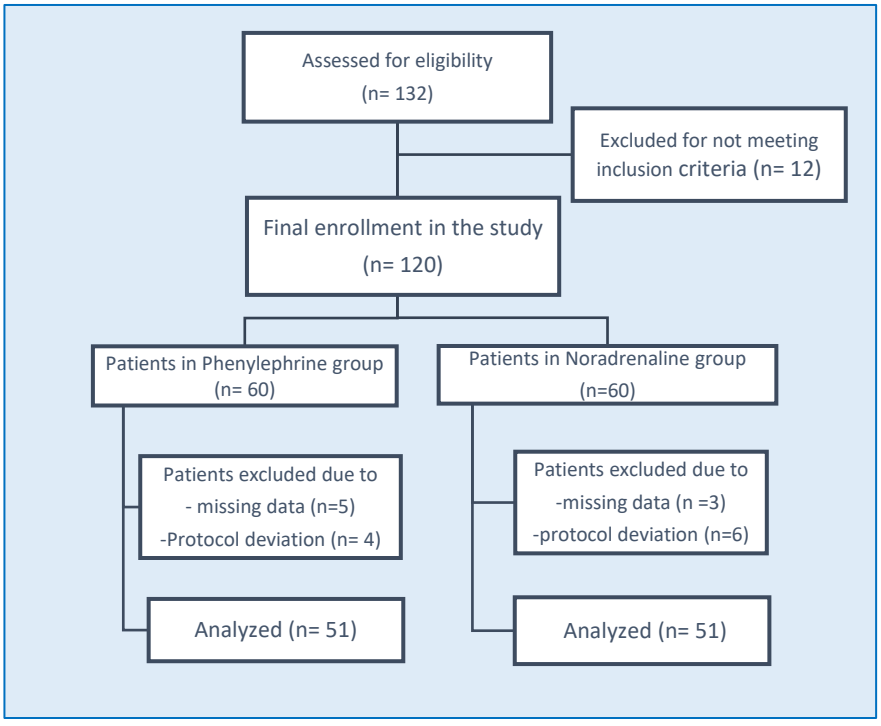

Figure 1: CONSORT flow diagram

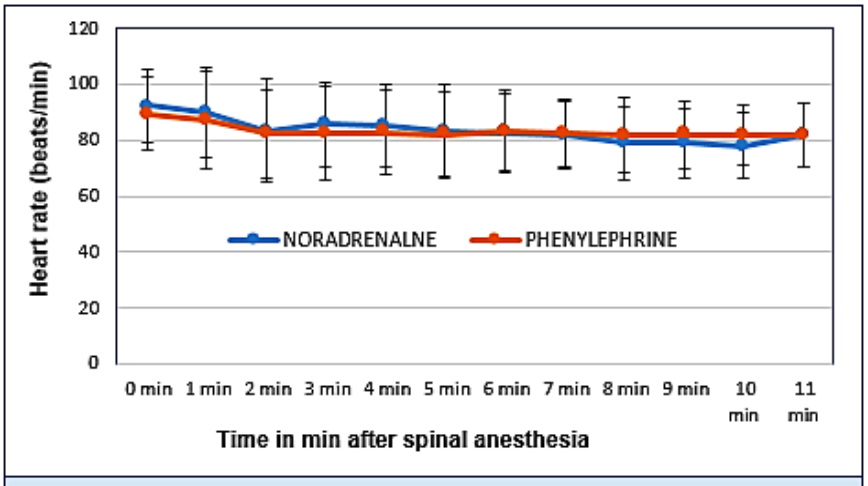

Figure 2: Comparative heart rates. Markers are means; error bars are SDs.

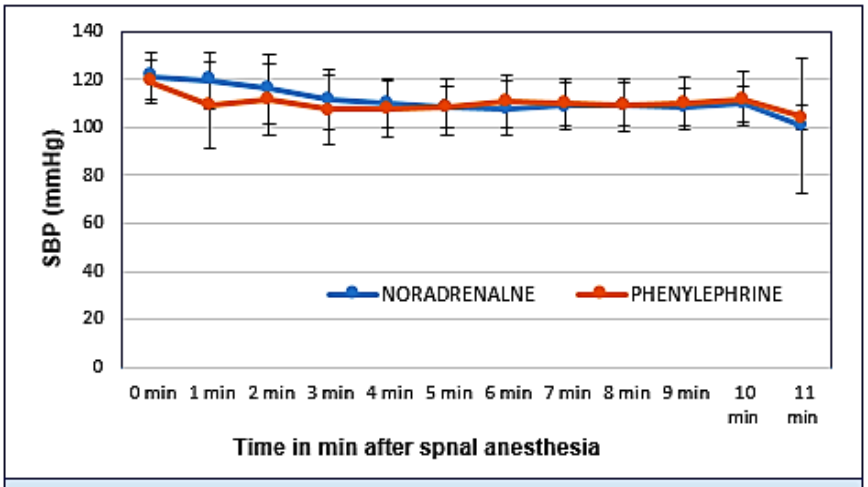

Figure 3: Comparative systolic blood pressures (mean ± SD)

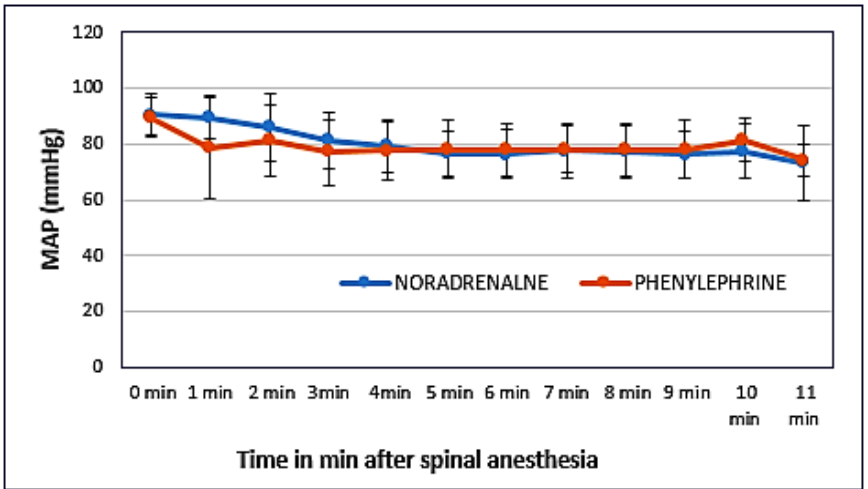

Figure 4: Comparative mean arterial pressures

mean HR values every minute post spinal till delivery of the baby. The difference in the values of primary outcome (maternal heart rates) in the two groups was statistically non-significant. Figures 3 and 4 show the men values of the baseline SBP and mean arterial pressure (MAP) values every minute post spinal till delivery of the baby. Mean SBP (119.6 vs. 109.2 mmHg), mean DBP (89.5 vs. 78.6 mmHg), and mean MAP (74.6 vs. 67.3 mmHg) values at one minute are statistically higher ($P < 0.05$) in patients receiving noradrenaline than phenylephrine group, but during the later part of the surgery this difference in the two groups were not statistically significant ($P > 0.05$).

Eighteen (36%) patients in the NA group and 21 (41%) patients in the PE group ($p = 0.406$) developed one or more episodes of hypotension between administration of the prophylactic dose and delivery of the baby (Table 2).

Four (8%) patients in the norepinephrine group and eight (16%) patients in the phenylephrine group (Table 2) ($p = 0.461$) developed one or more episodes of bradycardia, but only two patients in the phenylephrine group needed atropine to treat bradycardia which was statistically not significant ($p = 0.43$). Eight patients (16%) developed nausea in the noradrenaline group and while in the PE group ten (20%) patients complained of nausea ($p = 0.603$), four (8%) had an episode of vomiting in the NA group and eight (16%) had vomited in PE group (Table 2) ($p = 0.219$)

Table 2: Comparison of adverse events

Outcomes	Group Noradrenaline (N = 51)	Group Phenylephrine (N = 51)	P value
Hypotension	18 (36)	21 (41)	0.406
Hypertension	0 (0)	2 (4)	0.153
Bradycardia	4 (8)	8 (16)	0.461
Nausea	8 (16)	10 (20)	0.603
Vomiting	4 (8)	8 (16)	0.219

Data presented as n (%);chi-square test used for the difference in categorical variables

The total vasopressor needed in the NA group was 15.69 µg (< 2 bolus injections) and 323.53 µg (> 3 bolus injections) in the PE group (p < 0.001) (Table 3). Mean neonatal Apgar scores at 1 and 5 min were comparable in both groups. No neonate had a mean Apgar score of eight or less.

4. Discussion

Cardiovascular changes during pregnancy along with aortocaval compression make 70 to 80% of pregnant patients susceptible to severe hypotension under SA during CD.[12] Preloading or co-loading with crystalloids and colloids at the proper speed and volume with SA offers some benefit, though it is not completly protective due to rapid redistribution of ths fluids.

The exact mechanism of spinal induced hypotension (SIH) is complicated, but the knowledge about the loss of arteriolar tone and a significant fall of systemic vascular resistance (SVR) opened pathways to vasopressors for their therapeutic as well as prophylactic use for hypotension.[12] Recent guidelines of obstetric anesthesia (2018) in their consensus statement emphasized the early and liberal use of vasopressors to prevent maternal hypotension aiming to maintain SBP at ≥ 90% and avoid fall below 80% of the target baseline.[3,5] A dependable vasopressor with a faster onset of action with a beneficial effect on maternal hemodynamics and fetal wellbeing without affecting the placental perfusion became a priority.

Phenylephrine is still considered the drug of choice for preventing and treating hypotension during SA for a cesarean section, as after decades of use, ephedrine was found to increase the risk of fetal acidosis despite improving placental perfusion.[8] Phenylephrine being purely an α adrenergic drug, corrected SIH by increasing the SVR and mean blood pressure by producing intense adrenergic arteriolar vasoconstriction. The absence of β adrenergic effects in contrast to ephedrine with poor ionotropic and chronotropic support resulted in reflex bradycardia and fall in cardiac output but not to an extent to compromise uterine perfusion and fetal wellbeing.[9]

Noradrenaline, an endogenous catecholamine and a biosynthetic precursor of adrenaline with both α and β effects, became an interesting alternative to phenylephrine in obstetric anesthesia. The combined weak β adrenergic and potent α effects of noradrenaline produced adequate balancing of negative chronotropic effects improved cardiac output and less propensity to produce bradycardia compared to phenylephrine.[10,11,13]

Vasopressors can either be administered as infusions or as intermittent bolus doses. Infusion regimens provide better hemodynamic control with minimal physical intervention.[14] But many clinicians favour bolus dosing because of the ease of the technique, and limited or non- availability of infusion pumps in various centres.[15]

In the present observational study, we evaluated the maternal hemodynamic and neonatal effects of prophylactic intravenous boluses of phenylephrine and noradrenaline to prevent SIH in doses of 100 µg and 8 µg respectively. Divided into two groups (group PE and group NE) of 51 each, mean HR, SBP, and MAP were checked every minute from the administration of SA to baby extraction. Rescue boluses of both the drugs in the same initial doses were repeated every min when needed to prevent sustained hypotension and maintain the goal SBP>90% of baseline. We observed that the hemodynamic parameters between administration of SA and baby extraction could be effectively controlled in both the groups without maternal and fetal adverse effects. In the current study, the difference in maternal heart rates and blood pressure were statistically insignificant but may be clinically significant as we found most of the patients in the PE group showing lower heart rates compared to the NA group particularly in the first minute after administering SA. Similar study by Sharkey et al. compared intermittent boluses of 100µg phenylephrine with 6µg noradrenaline and concluded that the hemodynamic profile offered by noradrenaline is superior to phenylephrine with a 71% relative reduction in the incidence of bradycardia.[13]

In a computer-controlled variable rates infusion study, the pharmacokinetic parameters of infusions of 0-5 µg/min noradrenaline and 0-100 µg/min phenylephrine were compared and they found that noradrenaline causes less depression of HR and greater cardiac output compared to phenylephrine.[10] They also conducted a study comparing a manually controlled noradrenaline infusion 0-5 µg/min to intermittent boluses of 5 µg and confirmed both the methods were equally effective in

controlling SIH. Although they ended up with a larger dose of noradrenaline with infusion technique, but no maternal and neonatal adverse effects were noticed.[16]

The total dose of vasopressor required from induction of SA to delivery of the baby was significantly low in the NA group ($p < 0.001$) in line with Puthenveettil et al. study where they compared bolus doses of 50 µg phenylephrine and 4 µg noradrenaline. Noradrenaline was effective in treating spinal induced hypotension and the number of bolus doses required was significantly low compared to phenylephrine. [17] A fixed-rate infusion study done by Vallejo et al. comparing phenylephrine and noradrenaline found that noradrenaline was efficacious in preventing hypotension.[18] Although we used a slightly higher dose of 8 µg noradrenaline in our study, our results were comparable to the above studies as far as the maternal hemodynamics were concerned. Onwochei et al. used an up-down sequential allocation method and determined the ED 90 of noradrenaline to be 6 µg. [19] Meanwhile, Mohta et al. found that noradrenaline is 11 times more potent than phenylephrine and 100 µg of phenylephrine would be approximately equivalent to 9 µg of noradrenaline.[20]

There were no significant differences between the PE and NA groups concerning the incidence of hypotension induced nausea/vomiting, maternal hypertension, and similar findings have been reported by other authors.[13,16,17] In the present study, only two patients in the PE group required atropine for correction of bradycardia which was not statistically significant. The mild β effects of noradrenaline were found to be more effective in maintaining the heart rate and blood pressure which also correlates well with cardiac output.[10,11]

The comparison of the APGAR scores at 1 and 5 min was statistically insignificant in both the groups which were comparable to the other studies. Phenylephrine due to its pure α agonist effect produces reflex bradycardia and fall in cardiac output, which can result in poor APGAR scores in the already compromised fetus. Non assuring fetal status was an exclusion criterion in our study.

Regarding the safety of peripheral intravenous administration of vasopressors, studies have concluded that when used as dilute solutions for a limited duration under close observation, the complications are uncommon.[21,22]

5. Limitations

The study lacked randomization and double blinding but noth groups matched well with respect to the demographic variables. The benefits of noradrenaline and phenylephrine infusions in pregnant patients with comorbidities needs further evaluation. Umbilical arterial pH monitoring may be a desirable parameter in such studies, but the facility was not available at our institution. Same was the case with crdiac output monitoring, the facility not available.

6. Conclusion

Both study drugs – phenylephrine and noradrenaline, when used as prophylactic bolus in patients undergoing cesarean deliveries under spinal anesthesia, are effective in reducing the incidence of bradycardia, hypotensive episodes, and nausea, vomiting. However, noradrenaline is a slightly better economical alternative to phenylephrine for maintaining maternal hemodynamics and fetal safety.

7. Acknowledgments

None

6. Authors' contributions

All authors contributed in the conception of the idea, study design, analysis of the data, drafting the manuscript and the final approval.

9. Conflict of interest

No potential conflict of interest relevant to this article was reported.

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