Original Article

Comparison of the effect of intravenous phenylephrine and norepinephrine boluses for post-spinal hypotension on neonatal outcome in elective caesarean section: A randomised controlled trial

Address for correspondence:
Dr. Prerona Saha, Department of Anaesthesiology, Dhubri Medical College and Hospital, Dhubri, Assam, India.
E-mail: preronagn123@gmail.com

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Prerona Saha, Chandita Konwar, Aditya Pandey[1], Prabal Bharali[2]
Department of Anaesthesiology, Dhubri Medical College and Hospital, Dhubri, Assam, [1]Department of Community Medicine, MLB Medical College, Jhansi, UP, [2]Department of Anaesthesiology, Nagaon Medical College, Nagaon, Assam, India

ABSTRACT

Background and Aims: There is limited data on the effects of norepinephrine on neonatal outcomes and maternal complications relative to other vasopressors. The study aimed to compare neonatal outcomes and maternal complications after bolus intravenous doses of phenylephrine and norepinephrine for post-spinal hypotension in elective caesarean section women. **Methods:** This randomised study was done on 100 elective caesarean section women under spinal anaesthesia. Block randomisation divided women into two groups to receive intravenous phenylephrine 50 μg bolus (Group A) or norepinephrine 5 μg bolus (Group B) following post-spinal hypotension. Groups were evaluated and compared for umbilical arterial blood gas analysis, birth weight, APGAR (appearance, pulse, grimace, activity, and respiration) score, maternal haemodynamics, and complications. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to verify data normality. Independent samples *t*-test or Mann-Whitney U test was employed to compare continuous variables based on data normality, and the Chi-square test was used to determine categorical variable associations. **Results:** Demographic characteristics of women were found to be comparable between groups. Umbilical arterial potential of hydrogen, partial pressure of oxygen, partial pressure of carbon dioxide, base excess, bicarbonate, birth weight, and APGAR scores were comparable across groups, showing no significant differences ($P > 0.05$). Groups had similar maternal haemodynamic characteristics and episodes of nausea, vomiting, and chest pain across groups without statistical significance ($P > 0.05$). **Conclusion:** No notable distinction was found between neonatal outcomes and maternal complications between phenylephrine and norepinephrine bolus regimens. Norepinephrine can be used as an alternative to phenylephrine post-spinal hypotension in women undergoing elective caesarean section.

Keywords: APGAR score, caesarean section, hypotension, norepinephrine, phenylephrine, pregnancy, spinal anaesthesia, umbilical arterial blood gas analysis

INTRODUCTION

Phenylephrine has been identified as a potential vasopressor that has been preferred for the management of post-spinal hypotension in the context of caesarean section procedures.[1] One of the primary limitations of using phenylephrine is the occurrence of reflex bradycardia, which can lead to a decrease in cardiac output.[2] The potent vasopressor norepinephrine has

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strong agonistic effects on α-adrenergic receptors but relatively weaker agonistic effects on β-adrenergic receptors. Its direct positive chronotropic impact may also reduce bradycardia.[3] However, the effects of norepinephrine on neonatal outcomes and maternal complications compared to other vasopressors are still being studied.

The primary objective of the study was to compare neonatal outcomes by examining the umbilical arterial potential of hydrogen (pH) of neonates born to women who received either phenylephrine or norepinephrine to manage post-spinal hypotension during elective caesarean sections. Secondary objectives were to compare maternal haemodynamics, complications, and other neonatal parameters within both groups. The hypothesis tested in the study is to determine if there is any difference between phenylephrine and noradrenaline in terms of foetal outcomes and maternal haemodynamics when used as boluses as treatment for post-spinal hypotension.

METHODS

The present study, a hospital-based double-blinded randomised controlled trial, was initiated after institutional ethical committee approval (vide approval number MC/190/2007/Pt-11/Dec-2019/11, dated 11 December 2019). The study was registered with the Clinical Trials Registry-India (vide registration number CTRI/2020/06/026239, accessed from www.ctri.nic.in) and was conducted from July 2020 to July 2021. Each participant provided written informed consent for their involvement in the study and the use of their patient data for research and educational purposes. The study was conducted following the principles of the Declaration of Helsinki (2013) and good clinical practice.

Pregnant women posted for elective caesarean delivery under spinal anaesthesia who were 18 years of age or older, willing to participate in the study, having American Society of Anesthesiologists (ASA) physical status II, and having an uncomplicated singleton pregnancy were included in the study. Pregnant women with pre-existing medical conditions such as diabetes, hypertensive diseases, cardiovascular disease, cerebrovascular disease, and renal impairment were excluded. Participants with placenta praevia, foetal malformations, and those on prolonged drug therapy were also excluded from the study.

The participants were provided with a comprehensive explanation regarding the detailed procedure of the study. Block randomisation with blocks of varied sizes in a 1:1 ratio was used to ensure an equitable distribution of participants between the two groups by using a computerised random number list prepared before the trial began. The participants were randomised into Group A (phenylephrine) and Group B (norepinephrine). An assistant nurse facilitated the division of participants into various groups. Each participant was given an opaque, sealed envelope containing a random number by using a computerised random number list, along with their respective date of birth written on top. The participants were instructed not to open the envelope, and the accompanying hospital staff ensured compliance with this instruction. The treatment modality was applied depending on the group into which participants were randomised. Participants in group A received phenylephrine 50 μg intravenous (IV) bolus following post-spinal hypotension, while group B received norepinephrine 5 μg IV bolus following post-spinal hypotension.

The assistant's involvement in the study was discontinued to maintain blinding. Following the patient's transfer to the operation theatre, a junior resident assigned the task proceeded to unseal the envelopes. Subsequently, the resident prepared the study drugs in two syringes, ensuring they were identical, and allocated them to their respective study groups. For the phenylephrine group, an ampoule containing 10 mg phenylephrine was diluted to prepare a concentration of 50 μg/mL, which was then drawn in a 10-mL syringe and labelled as Group A. For the norepinephrine group, 1 mL containing 1 mg of norepinephrine was diluted to prepare a concentration of 10 μg/mL, drawn in a 10-mL syringe, and further diluted up to 5 μg per mL and labelled as Group B. The resident did not engage in any additional activities throughout the study. An IV line was established, and Ringer's lactate infusion was started. They received aspiration prophylaxis as per our institutional protocol: IV ondansetron (4 mg) and metoclopramide (10 mg) were administered. After recording the baseline haemodynamic parameters of the participants, spinal anaesthesia was administered by another resident anaesthesiologist, with the parturient in a left lateral position with the back parallel to the edge of the operating table, thighs flexed to the abdomen, and the neck flexed to allow the forehead to be as close as possible to the knees,

opening up the vertebral spaces. The L4-L5 interspace corresponding to the highest point of the iliac crest was identified. A 25-G Quincke's spinal needle was used to administer spinal anaesthesia in the L3-L4 space by midline approach. The stylet was removed after a loss of resistance was felt and when there was a visible free flow of cerebrospinal fluid. In accordance with institutional policy, a hyperbaric 0.5% bupivacaine solution was injected intrathecally at a volume of 2.2 mL for women with a height greater than or equal to 150 cm and a volume of 2.0 mL for women with a height less than 150 cm. Along with this, an injection of buprenorphine measuring 0.2 mL (equivalent to 60 μg) was provided at a rate of 0.2 mL/s.[4] Immediately after giving the drug, the needle was withdrawn. The patient was then turned supine, and a wedge was kept under her right buttock. IV co-loading was done with Ringer's lactate (15 mL/kg) at the time of giving the spinal injection. The surgery was commenced after confirming that the level of sensory block had reached the T6 level. The resident in question did not participate further in the trial. After administration of spinal anaesthesia, the time from spinal anaesthesia to delivery (in minutes), the time from uterine incision to delivery (in seconds), episodes of hypotension and bradycardia, total number of vasopressor boluses used until delivery, maternal side effects (such as nausea, vomiting, and chest discomfort), umbilical cord blood gas values including pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), base excess, and bicarbonate (HCO_3), neonatal birth weight, and APGAR (appearance, pulse, grimace, activity, and respiration) score[5] at 1 and 5 minutes were noted. The participation of another junior resident was enlisted to assist with intraoperative and postoperative evaluations of the parameters for the trial. The APGAR score of the baby was noted after its delivery by a paediatrician who was not further involved with the study.

Hypotension for the study was defined as a reduction of at least 20% from the initial systolic arterial pressure measurement or an absolute value below 100 mmHg.[4] Each episode of hypotension was treated by administering a 1 mL bolus of the study medication according to the group allocation. In the event of failure to achieve adequate spinal block or if the patient did not develop post-spinal hypotension, the study drug was discarded, and the patient was excluded from the study. The duration between the administration of spinal anaesthesia and the occurrence of delivery (DEL) was defined as the interval beginning from the moment the intrathecal drug injection was completed until the baby was delivered.[6] The time from uterine incision (UI) to DEL was defined as the time taken from a transverse incision in the lower segment of the uterus until the baby's delivery.[6] Nausea and vomiting were managed according to the institutional guidelines by a bolus dose of ondansetron 0.1 mg/kg, and any complaint of chest discomfort was managed by reassuring the patient, followed by IV Midazolam 0.01 mg/kg if needed.

The study's primary outcome was to compare the neonatal outcomes based on the umbilical arterial pH of newborns in parturient women who received phenylephrine or norepinephrine to manage post-spinal hypotension during elective caesarean section. The study's secondary outcomes were the impact on maternal heart rate and blood pressure and complications such as nausea, vomiting, chest discomfort, vasopressor usage, foetal arterial blood gas parameters, neonatal birth weight, and APGAR scores at 1 minute and 5 minutes. For determining the umbilical arterial pH of newborns, immediately after the baby's delivery, a segment of the umbilical cord was double-clamped before the baby's first breath as early as possible, and 1.5–2.0 mL of umbilical arterial blood sample was collected in a pre-heparinised syringe. The sample was sent immediately for analysis in an ice box, and the analysis was carried out as early as possible. The same sample was used to assess other foetal arterial blood gas parameters. The reference range of the umbilical arterial pH was 7.18–7.42; the umbilical arterial pO_2 was 6.43–29.43 mmHg, the umbilical arterial pCO_2 was 33.44–66.56 mmHg, the umbilical arterial HCO_3 was 15.60–30.70 mEq/L, and the base excess was 12.30–4.70.[7] The mother's systolic, diastolic, and mean arterial blood pressure were measured at various times, starting immediately after the spinal procedure and continuing at 3-minute intervals until the baby's delivery. The APGAR score of the baby was noted after its delivery at 1 minute and 5 minutes.

From a previous study,[4] considering a mean (standard deviation) umbilical cord blood pH of 7.33 (0.08) in women who received 100 μg phenylephrine, to detect a difference of 0.05 in pH with population variance of 0.064, considering the power of the study to be 80% and confidence interval of 95%, 41 women were required in each group. Regarding a possible dropout of 20%, 50 women were studied in each group, with a total sample size of 100 women.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) statistics software version 23.0 (Armonk, NY: International Business Machines Corp., USA) statistical software. The data were processed and coded in MS Excel. The normality of the data was checked using the Kolmogorov-Smirnov and Shapiro-Wilk tests Unpaired *t*-test was used to compare age, umbilical arterial pH, pO_2, pCO_2, mean arterial pressure (MAP), and heart rate, while Mann-Whitney U test was used to compare weight, height, duration of spinal anaesthesia to DEL, UI to DEL, base excess, umbilical arterial HCO_3, birth weight, and APGAR scores depending on the normality of the data. Fisher's exact test was applied to find associations between maternal complications and the treatment modality between the groups. A *P*-value of <0.05 was considered statistically significant at the 95% confidence interval.

RESULTS

Of the 100 participants enroled, 95 completed the study. For different reasons, five women were eliminated from the analysis [Figure 1]. The demographic characteristics of the women, including age, height, weight, and ASA physical status, and duration of surgical procedures were found to be similar between the two groups ($P > 0.05$) [Table 1].

In the two groups, the umbilical arterial pH, pO_2, pCO_2, base excess, HCO_3, neonatal birth weight, and APGAR scores at 1 minute and 5 minutes were comparable between the two groups ($P > 0.05$) [Table 2].

The maternal haemodynamic parameters [Figure 2] were comparable between the groups. The mean number of doses of vasopressors required in Group A was higher than in Group B but without statistical significance. Similar was the case with the incidence of nausea, vomiting, and chest discomfort, which were comparable between the groups without statistical significance ($P > 0.05$).

DISCUSSION

No notable distinction was found between neonatal outcomes assessed with umbilical arterial pH between intermittent phenylephrine and norepinephrine intravenous bolus regimens. There were no notable variations in umbilical artery HCO_3, pO_2, pCO_2, and base excess that reached statistical significance. No notable variations were observed in the APGAR

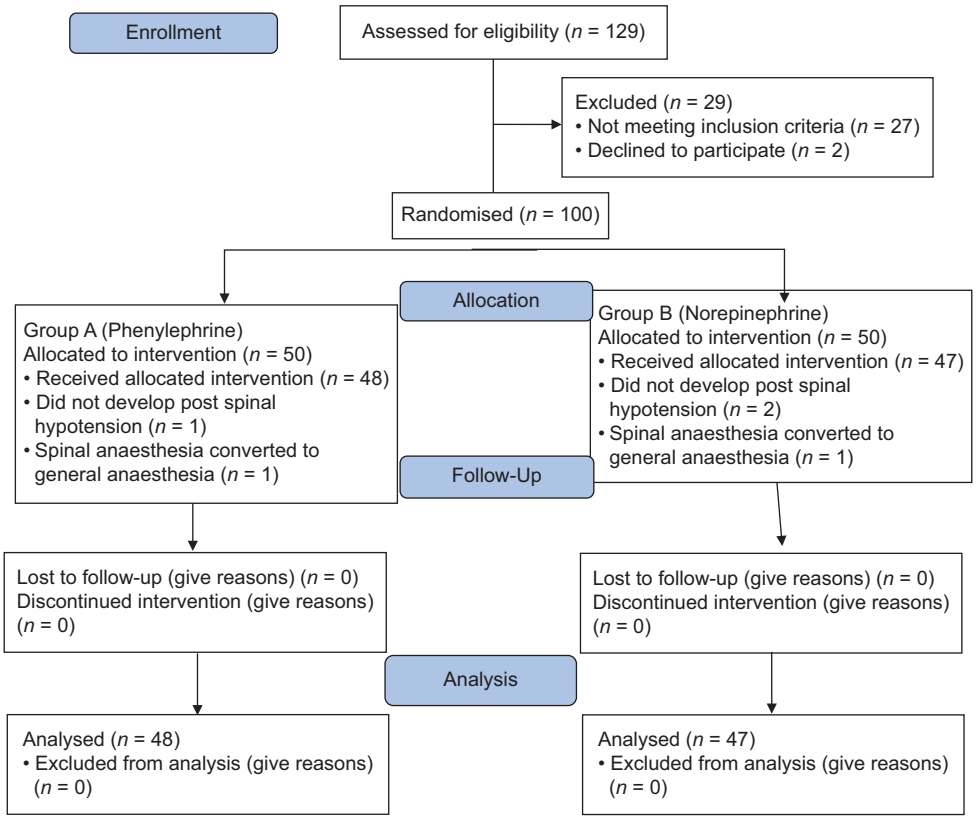

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram

scores at 1 minute and 5 minutes. There were no notable variations in neonatal birth weight, the number of vasopressor boluses administered, the duration from spinal anaesthesia to DEL, and the duration from UI to DEL. Thus, in our study, phenylephrine and noradrenaline boluses showed no significant difference in terms of neonatal outcome, maternal haemodynamics, and incidence of maternal complications when used as a treatment for post-spinal hypotension.

Sharkey AM *et al*.[6] also observed no statistically significant difference in umbilical artery pH when comparing intermittent IV boluses of 100 µg phenylephrine and 6 µg norepinephrine in elective caesarean section. Wang X *et al*.[8] and Cho *et al*.[9] relating to the administration of norepinephrine and phenylephrine boluses to address maternal hypotension during elective caesarean section revealed no statistically significant difference in the umbilical artery pH levels observed in either group. In contrast, a study by Mohta M *et al*.[4] showed that the umbilical artery pH was higher in cases where phenylephrine was administered than norepinephrine. This discrepancy highlights a potential difference in the impact of these two medications on the acid-base balance of neonates. The heterogeneity observed in the study can be ascribed to the prioritisation of maternal bradycardia as the primary outcome, which influenced the determination of the sample size. In addition, foetal acid-base status was considered a secondary outcome.

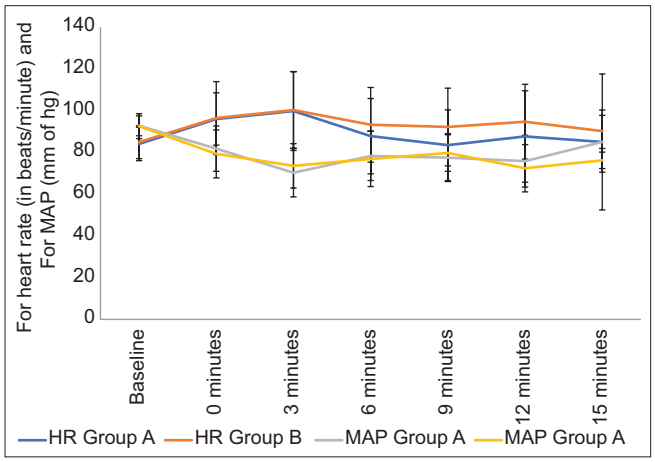

Figure 2: Distribution of haemodynamic parameters among participants of both the groups (P>0.05). Group A: phenylephrine, Group B: norepinephrine, HR: Mean heart rate in beats/minutes, MAP: Mean arterial pressure in mmHg

Table 1: Demographic variables of the participants

Parameter	Group A (*n*=48)	Group B (*n*=47)
Age (years)	26.12 (4.13)	26.32 (4.42)
Weight (kg)	64.94 (4.69)	64.70 (4.13)
Height (cm)	156.71 (2.76)	156.13 (1.78)
Gestational age (weeks)	38.48 (0.62)	38.36 (0.73)
Duration minutes		
SA to DEL	8.25 (2.62)	9.15 (3.27)
UI to DEL	67.21 (6.70)	67.55 (6.99)

Data represented as mean (standard deviation), *n*=number of patients, SA=Spinal anaesthesia, DEL=delivery, UI=uterine incision

Regarding APGAR scores, the results are the same as those of several other studies that compared boluses of norepinephrine and phenylephrine and found no statistically significant differences between the two groups.[4,6,8,9-11] Studies done by Wang X *et al*.,[8] Mohta M *et al*.,[4] and Cho WJ *et al*.[9] have all observed similar findings.

Sharkey AM *et al*.[6] also found no difference in the number of boluses of vasopressors from the time of spinal anaesthesia to the time of delivery, which is in line with our study. In contrast, in studies conducted by Puthenveettil N *et al*.[10] and Mohta M *et al*.,[4] the number of boluses was significantly higher in the phenylephrine group than in norepinephrine. No statistically significant difference was seen in the maternal haemodynamic parameters between the two groups. This finding aligns with the research done by Mohta M *et al*.[4] and Wang X *et al*.,[10] in which the haemodynamic parameters of both groups did not exhibit any statistically significant differences.

Table 2: Neonatal outcomes of the participants

Parameter	Group A (*n*=48)	Group B (*n*=47)	Mean difference (95% Confidence interval)	*P*
Umbilical arterial pH	7.27 (0.04)	7.29 (0.03)	−0.006 (−0.015–0.002)	0.184
Umbilical arterial PO_2	13.35 (5.52)	14.28 (5.10)	−1.134 (−3.284–1.016)	0.298
Umbilical arterial PCO_2	51.21 (8.06)	50.80 (8.75)	0.623 (−2.810–4.057)	0.719
Base Excess	−3.59 (1.38)	−3.54 (1.48)	−0.489 (−0.638–0.540)	0.856
Umbilical arterial HCO_3	23.23 (2.65)	24.04 (2.08)	−0.627 (−1.543–0.287)	0.177
Birth weight	2.91 (0.19)	2.85 (0.23)	0.059 (−0.028–0.147)	0.180
APGAR 1 minute	8.12 (0.44)	8.28 (0.49)	−0.133 (−0.327–0.060)	0.175
APGAR 5 minutes	8.87 (0.33)	8.94 (0.25)	−0.064 (−0.185–0.057)	0.298

Data represented as mean (standard deviation), pH=potential of hydrogen, pO_2=partial pressure of oxygen, pCO_2=partial pressure of carbon dioxide), HCO_3=bicarbonate, APGAR=appearance, pulse, grimace, activity, and respiration, *n*=number of patients

One of the limitations of our study is its reliance on data from a single hospital. Further evaluation of norepinephrine is warranted in cases of uteroplacental insufficiency, emergency caesarean sections, or in pregnant women with cardiac complications.

CONCLUSION

This study suggests no significant difference in neonatal outcomes based on the umbilical arterial pH when comparing intermittent bolus regimens of phenylephrine and norepinephrine in women who undergo elective caesarean sections under spinal anaesthesia.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Conflicts of interest

There are no conflicts of interest.

ORCID

Prerona Saha: https://orcid.org/0000-0002-9033-4797
Chandita Konwar: https://orcid.org/0009-0009-4693-4742
Aditya Pandey: https://orcid.org/0009-0000-6029-2621
Prabal Bharali: https://orcid.org/0009-0005-2180-3384

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