Original Article

Comparison of phenylephrine and norepinephrine for treatment of spinal hypotension during elective cesarean delivery- A randomised, double-blind study

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Abstract

Background and Aims: Hypotension following subarachnoid block for cesarean delivery (CD) is common. We compared the effect of bolus administration of norepinephrine and phenylephrine on umbilical artery pH (primary objective) and their efficacy for the treatment of maternal hypotension (secondary objective) in term parturients undergoing elective CD under spinal anesthesia.

Material and Methods: In a randomized, double-blinded study, parturients received 1 mL boluses of either phenylephrine 100 μg/mL (group phenylephrine; $n = 45$) or norepinephrine 7.5 μg/mL (group norepinephrine; $n = 45$) whenever maternal systolic blood pressure decreased to ≤80% of baseline. Maternal hemodynamic changes, vasopressor, and atropine requirement and neonatal outcome (umbilical cord blood gas analysis, Apgar scores, neonatal neurobehavioral response) were assessed.

Results: The Apgar scores and umbilical cord blood gas analysis were comparable between groups. The neurobehavioral scale score was significantly higher in group NE compared with that in group PE at 24 h and 48 h; $P = 0.007$ and 0.002, respectively. The number of vasopressor doses and time to the first vasopressor requirement for maintaining systolic pressure >80% of baseline was comparable in both groups. Incidence of bradycardia ($P = 0.009$), reactive hypertension ($P = 0.003$), and dose requirement of atropine ($P = 0.005$) was higher in group PE compared with group NE.

Conclusions: In term normotensive parturients who received bolus norepinephrine 7.5 μg or phenylephrine 100 μg for the treatment of post-spinal hypotension during CD, neonatal umbilical cord blood gas analysis and Apgar scores were comparable. Norepinephrine use was associated with a lower incidence of maternal bradycardia and reactive hypertension compared with phenylephrine.

Keywords: Anesthesia, hypotension, norepinephrine, phenylephrine, spinal

Introduction

Spinal anesthesia, the technique of choice for elective cesarean delivery (CD), is associated with maternal hypotension. Prolonged and severe maternal hypotension can cause uteroplacental hypoperfusion, fetal distress, and maternal nausea and vomiting.[1]

Phenylephrine, an α-adrenergic drug, is currently the vasopressor of choice for the prevention and management of post-spinal hypotension. However, phenylephrine has a dose-related tendency to decrease maternal heart rate and cardiac output (CO) that may adversely affect uteroplacental perfusion.[2,3] This concern has led to the consideration of alternative vasopressors. Norepinephrine is a potent

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α-adrenergic receptor agonist, but unlike phenylephrine, it is also a relatively weak β-adrenergic receptor agonist.[4] A computer-controlled infusion of norepinephrine maintained blood pressure as effectively as phenylephrine, but with less bradycardia and lesser fall in CO and no significant differences in neonatal outcomes.[4] It has been reported that norepinephrine fixed-rate infusion (0.05 μg/kg/min) can effectively prevent hypotension and can be considered as an alternative to phenylephrine (0.1 μg/kg/min).[5] Bolus dose of norepinephrine has also been used for management of post-spinal hypotension in elective CD.[6]

Prophylactic infusion of norepinephrine and phenylephrine as vasopressors for management of post-spinal hypotension in elective CD have been compared previously. However, literature comparing the use of these vasopressors as bolus dose for the treatment of post-spinal hypotension is limited.[7,8] More supporting data from randomized controlled trials are required before norepinephrine can replace phenylephrine as vasopressor of choice in obstetrics. We hypothesized that norepinephrine is a superior vasopressor as compared to phenylephrine for the treatment of post-spinal hypotension with regard to neonatal outcome (cord blood gas analysis, Apgar scores, and neonatal neurobehavioral scores) in term normotensive parturients undergoing elective CD under spinal anesthesia. The aim of this study was to compare the effect of bolus administration of norepinephrine and phenylephrine on umbilical artery pH (primary objective) and their efficacy for the treatment of maternal hypotension (secondary objective) in parturients undergoing elective CD under spinal anesthesia.

Material and Methods

After obtaining approval from the Institute Ethics Committee and written informed consent from patients, this prospective, randomized, interventional, double-blind study was conducted between April 2018 and January 2019. The study was registered with Clinical Trials Registry India (CTRI/2017/12/010829). The study included 90 American Society of Anesthesiologists physical status II normotensive women, with singleton term pregnancy, scheduled for elective CD under spinal anesthesia who developed intraoperative hypotension. Parturients with pre-existing or pregnancy-induced hypertension, excessive intraoperative bleeding, diabetes mellitus, known cardiovascular or cerebrovascular disease, weight <50 kg or >100 kg, height <140 cm and >170 cm, in labor, with known allergy to study medication or contraindication to spinal anesthesia, were excluded from the study. This manuscript adheres to the applicable Consolidated Standards of Reporting Trials guidelines [Figure 1].

Women were allocated randomly using a computer-generated random number table in blocks of ten to receive one of two vasopressor solutions whenever maternal systolic blood pressure would decrease to 80% of baseline or less. Group assignments were concealed within opaque envelopes that were opened before spinal anesthesia. Group PE received a 1-mL bolus of phenylephrine 100 μg/mL; Group NE received a 1-mL bolus of norepinephrine 7.5 μg/mL. Additional boluses were administered if the SBP remained at or below 80% of baseline. The study drugs were prepared in the operating room (OR) in 10-mL syringes by dilution in 5% dextrose by an anesthesiologist not involved in the study.

Patients fasted overnight. Each patient received antacid prophylaxis. In the OR, standard monitoring was instituted. Patients were positioned on the operating table in the supine position with left uterine displacement. Following a 5 min rest period, baseline blood pressure (BP) and heart rate (HR) were calculated as the mean of three successive readings measured 1 min apart. Baseline systolic BP (SBP) and 80% value of the baseline SBP was calculated.

An 18-gauge intravenous cannula was sited on a forearm vein. Spinal anesthesia was given in the left lateral position with 2 mL of bupivacaine 0.5% with fentanyl 10 μg using a 25-gauge disposable spinal needle in the L3–4 intervertebral space. The patients were then placed supine with left uterine displacement. At the start of intrathecal injection, rapid intravenous co-hydration with Ringer's lactate solution (15 mL/kg) was commenced after which the flow was reduced to a slow maintenance rate. HR and BP were recorded at 1 min intervals from induction of spinal anesthesia until delivery of the baby. The patients received one of the two vasopressor solutions according to group allocation whenever maternal SBP was ≤80% of baseline. Oxygen at 5 L/min was administered via facemask.

The sensory block (alcohol swab) and motor block (modified Bromage scale)[9] were assessed and recorded at 5 and 15 min after intrathecal injection. Sensory block to T5 dermatome was considered adequate for surgery.

The incidence of hypotension (SBP ≤80% of baseline), reactive hypertension (SBP ≥120% of baseline), bradycardia (HR <60 beats/min), HR <45 beats/min, and maternal tachycardia (HR >100 beats/min) was recorded. The period from onset of hypotension until its correction was considered as one hypotensive episode. Recurrence of hypotension after one or more normal SBP values was considered as the next hypotensive episode. Atropine 0.6 mg

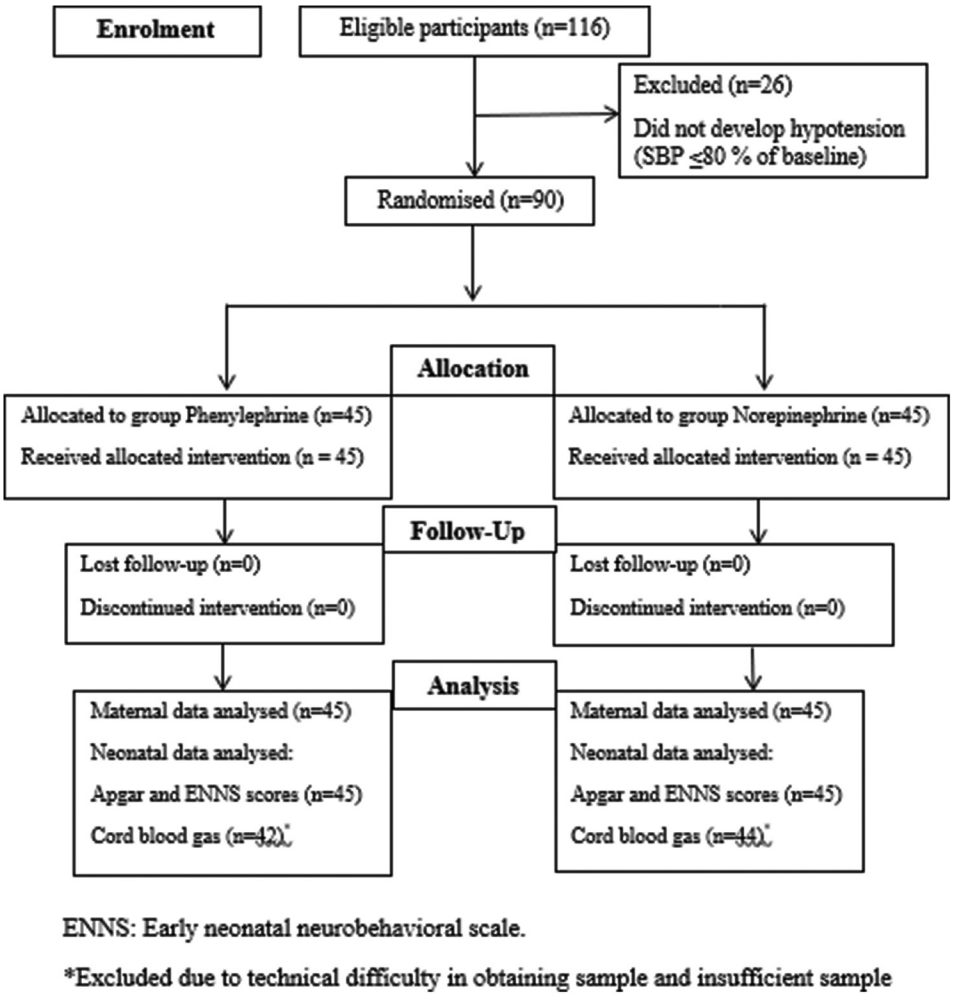

Figure 1: CONSORT flow diagram

IV was administered if there was bradycardia associated with SBP ≤80% of baseline or HR <45 beats/min regardless of SBP.

The number of hypotensive and bradycardia episodes, number of vasopressor doses needed to treat the first hypotensive episode, time of first vasopressor administration, the total number of doses and total dose of vasopressor administered, atropine requirement, and its relation with vasopressor administration was noted. The duration of hypotension and reactive hypertension was recorded.

The induction-to-skin incision interval, induction-to-delivery interval, incision-to-delivery interval, and uterine incision-to-delivery interval were noted. The occurrence of nausea (none, mild, moderate, or severe), retching, and vomiting was noted. After delivery, oxytocin 2 U was given by slow IV injection followed by 10 U infusion. Umbilical arterial (UA) and umbilical venous (UV) blood samples were collected from a double-clamped segment of the umbilical cord for blood gas analysis. Apgar scores at 1, 5, and 10 min were determined by the attending pediatrician who was unaware of the group assignment. Weight of the newborn, time of onset of sustained rhythmic respiration, need for resuscitation, requirement for positive pressure ventilation (PPV) and duration of PPV, if required, and need for admission to the neonatal intensive care unit (NICU) was noted. The neurobehavioral response of the neonate was assessed at 2–4, 24 ± 2, and at 48 ± 2 h of age by a modified Early Neonatal Neurobehavioral Scale (ENNS).[10] This examination involves an assessment of neonatal reflexes, response to stimuli such as sound and pinprick, evaluation of the general body and truncal tone, and general alertness. The anesthesiologist performing neurobehavioral assessment was trained by a pediatrician before initiation of the study and was blind to group allocation.

Statistical analysis: Statistical analysis was performed by the Statistical Package for Social Sciences program for Windows, version 17.0 (SPSS, Chicago, IL). Continuous

variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentages. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired *t*-test, whereas the Mann–Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the Chi-square test or Fisher's exact test. For all statistical tests, a P value <0.05 was taken to indicate a significant difference.

With reference to a previous study, the median umbilical artery pH (UA pH) was 7.29 in the PE group and 7.30 in the NE group.[4] Since the distribution was normal (mean = median), the mean in the PE group and NE group was the same as the median value. The total sample size was calculated as 41 per group with a power of 90%, an α of 0.05 where the standard deviation of two groups was assumed 0.07 to detect a minimum of mean difference of 0.05 between two groups. Assuming a 10% dropout rate, the total sample size was set at 90 (45 per group). The primary outcome measure was UA pH. The secondary outcome measures included the number of episodes of maternal hypotension and reactive hypertension; vasopressor and atropine requirement; maternal nausea, vomiting, dizziness; Apgar scores and neonatal neurobehavioral scores.

Results

A total of 116 women presenting for elective CD under spinal anesthesia were assessed for eligibility. Twenty-six patients did not develop hypotension and hence did not require vasopressor. These patients were excluded from the study. The randomization code was not broken and the same code was used for the next eligible parturient. A total of 90 patients, who developed hypotension, participated in the study. Figure 1 shows the flow of participants in the randomized trial. Due to technical difficulties, UA sample could not be collected in three patients in group PE and one patient in group NE. UV sample from one patient in group PE was insufficient.

Patient characteristics, baseline hemodynamic data, and dermatomal sensory levels were comparable in both groups [Table 1]. Maternal hemodynamic data are presented in Table 2. Trends in SBP and HR are shown in Figures 2 and 3. The change in SBP from baseline was comparable except at time points T6 (P = 0.010), T7 (P = 0.016), and T8 (P = 0.009). The incidence and duration of reactive hypertension were greater in group PE compared with group NE; P = 0.003 and P = 0.006, respectively. The decrease in HR (beats/min) from baseline in group PE (14.96 ± 19.97) was significantly greater than that in group NE (5.02 ± 17.74), P = 0.014. The incidence of nausea (17.8% vs. 8.9%), retching (2.2% vs. 0%), and vomiting (2.2% vs. 6.7%) was comparable in groups PE and NE, respectively; all P > 0.05. Women in group PE experienced a higher incidence of dizziness (17.8%) compared with women in group NE (2.2%); P = 0.030. All parturients who experienced HR <45 beats/min reported dizziness.

Neonatal data are summarized in Table 3. There were no significant differences in gestational age, birth weight, and time to onset of sustained rhythmic respiration between groups. Apgar scores at 1, 5, and 10 min and umbilical cord blood gas analysis were comparable. No neonate required PPV, resuscitation, or had an Apgar score <7 at any time point. No UA pH values were <7.20. One neonate each in group PE and group NE required admission to NICU. The neurobehavioral scores at 2–4, 24, and 48 h are presented in Table 4. Total neurobehavioral scores were comparable between the groups at 2–4 h; P = 0.057 [Table 5]. Neonates whose mothers received norepinephrine exhibited statistically significantly higher total neurobehavioral scores at 24 h (P = 0.007) and 48 h (P = 0.002) compared with neonates whose mothers received phenylephrine.

Discussion

Our results demonstrate that neonatal outcome with regard to umbilical cord blood gas analysis and Apgar scores at 1, 5, and 10 min were comparable in neonates whose mothers received norepinephrine 7.5 μg or phenylephrine 100 μg as vasopressors for the treatment of post-spinal hypotension in term normotensive parturients undergoing CD under spinal anesthesia. Neonates whose mothers were treated with norepinephrine exhibited significantly higher neurobehavioral scores at 24 and 48 h compared with neonates whose mothers received phenylephrine.

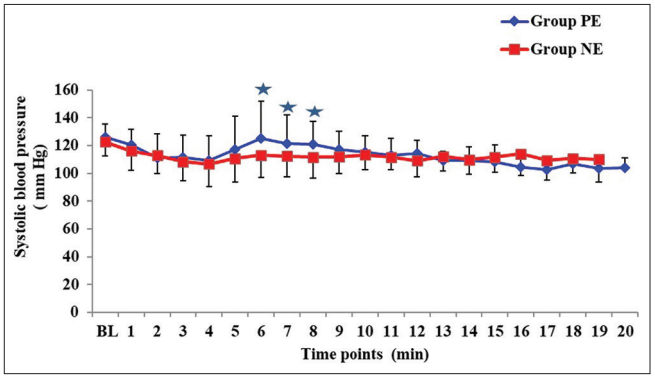

Figure 2: Trends in systolic blood pressure in the first 20 min after induction of spinal anesthesia. Footnote: BL-baseline, T1 to T20: time points 1–20 min after induction of spinal anesthesia

Apgar scores at 1, 5, and 10 min and umbilical cord blood gas analysis were comparable between phenylephrine and norepinephrine groups. No neonate had an Apgar score <7 at any time point or umbilical artery pH <7.2. Other studies have also reported no significant differences in neonatal outcomes with regard to Apgar scores and cord blood gases.[4,5,11] In contrast, a recent study found umbilical artery pH, bicarbonate, and base excess to be lower with the use of noradrenaline (5 μg) than phenylephrine (100 μg) with comparable Apgar scores.[12] They attributed this to placental transfer and β-agonist-mediated stimulation of fetal metabolism by norepinephrine. The incidence of neonatal acidosis (umbilical artery pH <7.2) was comparable between the groups.[12]

The effect of intrapartum drug exposure on the newborn has been evaluated by neurobehavioral assessment.[10] The ENNS devised by Scanlon comprises 15 observations of reflexes, muscle tone, and habituation to light and sound. Unlike the Brazelton scale,[13] the ENNS does not arouse the neonate or elicit its maximal response. We used the ENNS to assess the newborns at 2–4, 24, and 48 h. The ENNS scores improved with time in both the groups, suggesting that the effects of medications administered to mothers on neonates decreased with time. The total neurobehavioral scale score was significantly higher at 24 h (31.20 ± 0.97 and 30.5 ± 1.16, respectively) and 48 h (31.64 ± 1.03 and 30.87 ± 1.31) in neonates whose mothers received norepinephrine compared with those whose mothers received phenylephrine. The reason for this is unclear. However, the differences were small, neurobehavioral scores were not the primary outcome of the study, and there is a possibility of type 1 statistical error. Further investigation is required to confirm this observation. Prakash *et al.*[14] used the ENNS score in their study comparing the efficacy of phenylephrine 100 μg versus ephedrine 6 mg and found no difference in neurobehavioral scores between the treatment groups.

Both phenylephrine and norepinephrine were effective in treating maternal hypotensive episodes to within 80% of baseline SBP in our study. Systolic BP was comparable in the two groups at all time points, except at 6–8 min; however, SBP remained within the normal range in both the groups.

Limited studies have evaluated norepinephrine 7.5 μg and phenylephrine 100 μg administered as a bolus for the treatment of maternal post-spinal hypotension.[7,8] Wang *et al.*[7] reported that bolus dose of norepinephrine (4 μg), phenylephrine (50 μg), and ephedrine (4 mg) were all effective in treating post-spinal hypotension in women with preeclampsia undergoing CD. Parturients receiving norepinephrine experienced fewer episodes of bradycardia (3.6%) compared with those receiving phenylephrine (21.8%).[7] In our study, the incidence of bradycardia was 8.9 and 33.3% in parturients receiving norepinephrine and phenylephrine, respectively. This is possibly explained by the difference in the doses

Table 1: Patient characteristics, baseline hemodynamic data, dermatomal sensory level, and surgical times

	Phenylephrine (*n*=45)	Norepinephrine (*n*=45)
Age (year)	25.8±4.0	26.4±4.3
Weight (kg)	64.0±8.5	63.6±7.7
Height (cm)	157.1±5.1	156.9±4.9
Body mass index (kg/m^2)	25.9±3.1	25.9±2.7
Baseline heart rate (beats/min)	95.8±12.7	92.2±13.2
Baseline SBP (mmHg)	126.3±9.3	122.6±10.0
Block height at 5 min	T6 (T6-T7)	T6 (T6-T6)
Block height at 15 min	T4 (T4-T4)	T4 (T4-T5)
Induction-skin incision (min)	5.12±2.9	4.9±2.1
Induction-delivery (min)	12.4±5.7	11.4±2.9
Incision-delivery (min)	6.9±3.7	6.5±2.5
Uterine incision-delivery (s)	65.3±34.9	65.4±31.2

T: Thoracic dermatome; SBP: systolic blood pressure. Values are mean±SD or median (interquartile range), as appropriate

Table 2: Maternal hemodynamic data

	Phenylephrine (*n*=45)	Norepinephrine (*n*=45)	*P*
Heart rate <60 beats/min	15 (33.3)	4 (8.9)	0.009
Heart rate <45 beats/min	8 (17.8)	1 (2.2)	0.030
Heart rate >100 beats/min	0 (0)	0 (0)	-
Bradycardia + hypotension (n)	2 (4.4)	0 (0)	0.494
Number of vasopressor doses	1 (1-1) [1-3]	1 (1-1) [1-4]	0.161
Time to first vasopressor (min)	5.20±4.97	4.40±2.07	0.584
Atropine requirement (mg)	0.07±0.15	0.01±0.04	0.005
Minimum systolic pressure (mmHg)	91.36±12.57	91.36±8.65	1.000
Maximum systolic pressure (mmHg)	140.2±23.16	127.44±13.08	0.002
Duration of hypotension (min)	1.29±0.63	1.29±0.55	0.475
Reactive hypertension	13 (28.9)	2 (4.4)	0.003
Reactive hypertension duration (min)	1.69±0.75	1.00±0.0	0.006

Values are number (%), mean±SD or median (inter-quartile range), as appropriate

of norepinephrine (7.5 μg vs. 4 μg) and phenylephrine (100 μg vs. 50 μg) used in the two studies. Sharkey *et al.*[8] compared intermittent boluses of phenylephrine 100 μg and. norepinephrine 6 μg for prevention and treatment of maternal spinal-induced hypotension during elective CD. Outcomes were comparable with regard to hypotension, hypertension, tachycardia, nausea, and vomiting. The incidence of bradycardia was significantly lower in patients receiving norepinephrine compared with those receiving phenylephrine (10.9% vs. 37.5%) with the risk of multiple episodes of bradycardia (≥2 episodes) being significantly higher with phenylephrine (19.6%) compared with norepinephrine (21.4%).[8] Intermittent bolus norepinephrine (8 μg) provided a greater CO and a lower incidence of bradycardia compared with phenylephrine 100 μg for prophylactic management of maternal hypotension during elective CD with spinal anesthesia.[15] In another study,

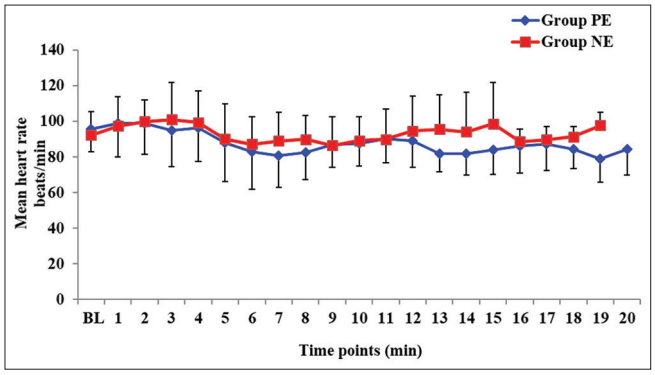

Figure 3: Trends in heart rate in the first 20 minutes after induction of spinal anesthesia Footnote: BL-baseline, T1 to T20: time points 1–20 min after induction of spinal anesthesia

bolus doses of phenylephrine 100 μg and norepinephrine 5 μg were found to have similar efficacy for the treatment of post-spinal hypotension during elective CD, with no difference in the incidence of maternal bradycardia (37.8% with phenylephrine vs. 22.2% with noradrenaline.[12] The authors acknowledged the possibility that their sample size was not large enough to identify a true difference in the incidence of bradycardia.[12]

In the present study, despite a similar efficacy between phenylephrine and norepinephrine for the treatment of maternal hypotension, there was a statistically significant difference in the incidence of bradycardia (33.3% vs. 8.9%, respectively) and reactive hypertension (28.9% vs. 4.4%, respectively). A significantly greater number of patients receiving phenylephrine (17.8%) experienced a decrease in HR <45 beats/min compared with those receiving norepinephrine (2.2%). This necessitated significantly increased atropine requirement in the phenylephrine group (0.07 ± 0.15 mg) compared with the norepinephrine group (0.01 ± 0.04); $P = 0.005$. The higher incidence of dizziness in the phenylephrine group is possibly related to HR <45 beats/min in the phenylephrine group compared with the norepinephrine group. Phenylephrine-induced reactive hypertension and bradycardia decrease CO that can adversely affect uteroplacental perfusion and be detrimental to both maternal safety and fetal well-being.[16]

Studies investigating norepinephrine and phenylephrine administered as a bolus[6,11] or infusion[4,5,17] for prophylaxis

Table 3: Neonatal data

	Phenylephrine (*n*=45)	Norepinephrine (*n*=45)	*P*
Gestational age (weeks)	38.9±1.2	38.3±1.5	0.057
Birth weight (kg)	2.7±0.2	2.7±0.3	0.803
Onset of respiration (s)	8.3±4.62	10.1±5.41	0.106
Onset of rhythmic respiration <90 s	45 (100)	45 (100)	-
Apgar scores at 1 min	8 (8-9)	9 (8-9)	0.312
5 min	9 (8-9)	9 (8-9)	0.650
10 min	9 (8-9)	9 (8-9)	0.161
Umbilical arterial acid-base status			
pH	7.27±0.05	7.30±0.05	0.128
PO_2 (mmHg)	15.45±7.63	16.49±7.62	0.530
PCO_2 (mmHg)	47.63±12.60	47.97±10.99	0.894
HCO_3 (mEq/L)	20.52±3.40	22.70±9.06	0.148
Base deficit (mEq/L)	(−) 3.14±2.27	(−) 3.13±2.55	0.979
Umbilical venous acid-base status			
pH	7.31±0.05	7.32±0.04	0.517
PO_2 (mmHg)	23.41±8.43	25.53±7.21	0.204
PCO_2 (mmHg)	41.07±10.05	39.90±10.86	0.597
HCO_3 (mEq/L)	19.33±3.83	24.5±30.45	0.266
Base deficit (mEq/L)	(−) 3.09±2.41	(−) 3.07±2.62	0.965

Values are mean±SD or median (range), as appropriate

Table 4: Early neonatal neurobehavioral scores at 2-4 h, 24 h and 48 h

Variables	2-4 h		*P*	24 h		*P*	48 h		*P*
0/1/2/3	PE (*n*=45)	NE (*n*=45)		PE (*n*=45)	NE (*n*=45)		PE (*n*=45)	NE (*n*=45)	
Response to pinprick	0/0/3/42	0/0/6/39	0.50	0/0/0/45	0/0/1/44	1.00	0/0/4/41	0/0/2/43	0.68
Pull to sitting	0/0/21/24	0/0/14/31	0.13	0/0/3/42	0/0/7/38	0.32	0/0/5/40	0/0/4/41	1.00
Arm recoil	0/0/10/35	0/0/14/31	0.48	0/0/4/41	0/0/5/40	1.00	0/0/10/35	0/0/14/31	0.60
General body tone	0/0/22/23	0/0/20/25	0.67	0/1/13/31	0/0/12/33	0.58	0/0/13/32	0/0/6/39	0.12
Truncal tone	0/0/20/25	0/0/15/30	0.28	0/0/13/32	0/0/9/36	0.33	0/0/11/34	0/0/4/41	0.09
Rooting	0/0/3/42	0/0/4/41	1.00	0/0/5/40	0/0/3/42	0.43	0/0/5/40	0/0/2/43	0.43
Sucking	0/0/11/34	0/0/4/41	0.09	0/0/6/39	0/0/7/38	1.00	0/0/5/40	0/0/3/42	0.71
Moro's reflex	0/0/23/22	0/0/16/29	0.14	0/1/13/31	0/0/9/36	0.35	0/0/12/33	0/0/7/38	0.20
Response to sound	0/4/20/21	0/2/18/25	0.57	0/1/16/28	0/0/14/31	0.53	0/3/9/33	0/0/13/32	0.15
Placing	0/0/19/26	0/0/6/39	0.002	0/0/13/32	0/0/6/39	0.07	0/0/7/38	0/0/1/44	0.05
Alertness	0/0/10/35	0/0/15/30	0.24	0/0/18/27	0/0/10/35	0.07	0/0/16/29	0/0/11/34	0.25

Values are numbers

Table 5: Total neonatal neurobehavioral score at 2-4, 24 and 48 h

	Phenylephrine (*n*=45)	Norepinephrine (*n*=45)	*P*
Total score 2-4 h	29.36±1.30	29.93±1.53	0.057
Total score 24 h	30.58±1.16	31.20±0.97	0.007
Total score 48 h	30.87±1.31	31.64±1.03	0.002

Values are mean±SD

against maternal post-spinal hypotension have reported similar efficacy for the prevention of hypotension. Ngankee *et al.*[4] reported that when the vasopressors were administered prophylactically at induction of spinal anesthesia by computer-controlled infusion, maternal CO and HR were greater in women treated with norepinephrine compared with those treated with phenylephrine. In a study comparing prophylactic norepinephrine bolus with phenylephrine bolus for prevention of spinal hypotension, CO and HR were observed to be greater in patients receiving norepinephrine bolus compared with those receiving phenylephrine bolus.[11] In contrast, Vallejo *et al.*[5] found that HR, incidence of bradycardia, BP, CO, cardiac index, stroke volume, and systemic vascular resistance were similar between groups receiving fixed-rate continuous infusion of phenylephrine (0.1 μg/kg/min) and norepinephrine (0.05 μg/kg/min) for prevention of post-spinal hypotension during elective CD. The reason for this discrepancy is that the authors have used a potency ratio of phenylephrine and norepinephrine of approximately 2:1, whereas this ratio has been determined as 13:1.[18]

Prevention and/or prompt treatment of maternal hypotension is important to prevent fetal acidosis and hypoxia. Phenylephrine, the current vasopressor of choice in obstetric anesthesia, causes arteriolar vasoconstriction and increases systemic vascular resistance and mean arterial pressure through its pure α-adrenergic agonist properties. Its use is associated with baroreceptor-mediated reflex bradycardia and a decrease in CO.[3] Norepinephrine has weak β-receptor agonist activity in addition to being an α-adrenergic agonist. It has both direct positive chronotropic and reflexive negative chronotropic actions, the overall effect being a neutral HR.[19] This pharmacological property gives norepinephrine an advantage over phenylephrine in obstetric anesthesia as it is less likely to decrease HR and CO. The doses chosen in our study were based on information from Ngankee[18] (personnel communication) who found that the estimated dose equivalent to phenylephrine 100 μg was norepinephrine 7.6 μg.

There is considerable research on methods of vasopressor administration; prophylactic versus treatment purpose and vasopressor infusion versus bolus administration. Prophylactic administration of vasopressors is associated with the use of relatively large doses compared with as-required use of vasopressor.[14] In our study, the mean total dose of phenylephrine required to treat SBP ≤80% of baseline was 128.9 ± 62.6 μg and that of norepinephrine was 9.0 ± 4.1 μg. In contrast, Chen *et al.*[20] investigated prophylactic norepinephrine infusion regimens of 5, 10, and 15 μg/kg/h whenever SBP <80% of baseline. The total dose of norepinephrine required was 106.0 ± 44.7 μg, 220.9 ± 74.6 μg, and 258.1 ± 115.1 μg, respectively.[20] In addition, the use of prophylactic infusions of vasopressors unnecessarily exposes those patients who are not prone to develop hypotension to vasopressor with the potential for adverse effects.[21] The amount of vasopressor administered by infusion to treat maternal hypotension is greater compared with a bolus dose. Doherty *et al.*[22] compared phenylephrine infusion (120 μg/min) versus bolus regimen (120 μg) on 60 women during CD under spinal anesthesia. The total dose of phenylephrine administered by infusion was higher (1740 ± 613 μg) compared with the bolus regimen (964 ± 454 μg).[22] Bolus administration of vasopressor is a simple and rapid method that can be easily

applied by anesthesiologists with minimal need for complex devices for the treatment of spinal hypotension.

The strength of this randomized controlled study is the comprehensive evaluation of neonatal outcome following bolus administration of norepinephrine and phenylephrine for treatment of post-spinal hypotension. Our study establishes the safety of norepinephrine as a vasopressor in the obstetric population.

Our study has limitations. Our data relate to women undergoing elective CD and the results cannot be extrapolated to emergency CDs. We did not measure CO in our study which would be more informative.

To conclude, term normotensive parturients undergoing CD under spinal anesthesia who received bolus norepinephrine 7.5 μg or phenylephrine 100 μg as vasopressors for the treatment of post-spinal hypotension had a similar neonatal outcome with respect to umbilical artery pH on cord blood gas analysis and Apgar scores. Norepinephrine use was associated with a lower incidence of maternal bradycardia and reactive hypertension compared with phenylephrine.

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Conflicts of interest

There are no conflicts of interest.

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