DOI: 10.7860/JCDR/2023/64470.18138

Original Article

Anaesthesia Section

Efficacy of Prophylactic Norepinephrine and Phenylephrine Infusions against Spinal Hypotension during Lower Segment Caesarean Section- A Randomised Clinical Study

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ABSTRACT

Introduction: Hypotension after Subarachnoid Block (SAB) can affect mother and foetus and can be prevented by prophylactic use of vasopressors. Phenylephrine (PE) has been a popular and effective drug as prophylaxis against hypotension. Norepinephrine (NE) is recently tried for this purpose.

Aim: To compare PE infusion with NE infusion prophylactically against SAB induced hypotension during Lower Segment Cesarean Section (LSCS).

Materials and Methods: This randomised clinical study was conducted in the Department of Anaesthesiology at a Tertiary Care Hospital, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka, India. The duration of the study was 12 months, from December 2018 to November 2019. A total of 156 primigravida and multigravida with singleton term pregnancy, posted for caesarean section under SAB received prophylactic infusions of either NE 5 µg/minute (group NE) or PE 50 µg/minute (group PE) immediately after SAB till end of the surgery. The primary outcome of the study was to assess the incidence of hypotension. The secondary outcomes included incidence of nausea, vomiting, hypertension, tachycardia, bradycardia and the neonatal outcomes. Related categorical and numerical variables were subjected to suitable statistical tests and analysed using Statistical Package for Social Sciences (SPSS) version 20.0.

Results: The mean age of the study participants of group NE was 24.47±2.52 years and group PE was 23.91±2.63 years, respectively. The age, parity and surgical duration was comparable between the groups. The incidence of hypotension was 17.9% in group NE and 26.8% in group PE (p-value=0.182). No significant differences in total doses of vasopressors used were noted. The incidence of bradycardia in group NE was 3.8% and 21.8% in the group PE (p=0.053). No adverse events or neonatal outcomes were observed.

Conclusion: The incidence of hypotension and the total dose of vasopressors administered were similar in the two groups receiving prophylactic infusion doses (NE or PE). Incidence of bradycardia was greater in the parturients receiving PE infusion.

Keywords: Bradycardia, Pregnancy, Subarachnoid block, Vasopressors

INTRODUCTION

The SAB has been widely accepted as an anaesthetic of choice for LSCS delivery due to its rapidity of onset, intensity with effective sensory and motor blockade. The risks associated with general anaesthesia such as airway and full stomach issues, uterine, foetal and neonatal adverse events are avoided. It also facilitates early bonding between mother and baby besides providing postoperative analgesia [1,2]. However, SAB induced sympathetic blockade causes maternal hypotension with potential for adverse maternal and foetal outcomes such as low perfusion pressures manifesting as maternal dizziness, nausea, vomiting, foetal hypoxia and foetal acidosis. Hence, prevention and treatment of hypotension has been a concern for both anaesthesiologists and obstetricians [2]. Hypotension can be prevented and treated by reversing the underlying physiologic changes like decreased Systemic Vascular Resistance (SVR), preload and Cardiac Output (CO) with the help of crystalloid or colloid preloading or co-loading, and prophylactic or therapeutic use of vasopressors [2-5].

The ideal vasopressor for infusion must have faster onset of action, consistent activity and have favourable effects on maternal haemodynamics, placental and foetal perfusion and be accessible. But there is a controversy as to which is the ideal drug [2]. PE has been most promising agent which has been used to combat spinal hypotension during LSCS. It is a potent α-adrenergic receptor agonist without β-adrenergic action causing arterial vasoconstriction which thereby, increases SVR and hence, the preload. It has been used prophylactically and therapeutically in terms of infusion and bolus doses. It has been effective in preventing foetal hypoxia and acidosis besides reducing maternal nausea and vomiting but it is usually associated with reflexive slowing of maternal Heart Rate (HR) resulting in decrease in CO, which may be a potential harm to the compromised foetus [2,6]. NE also has potent α-adrenergic receptor agonist activity and is used to treat spinal hypotension in the recent years. The weak β-adrenergic agonist activity may be useful to counteract pure vasoconstriction, with better precision in Blood Pressure (BP) control and higher CO for the mother and better umbilical cord pH and lower catecholamine levels for the neonate by lower incidences of bradycardia than PE [7-10]. Different dilutions (5 µg/mL of NE or 100 µg/mL of PE) (7) and bolus doses and fixed rate infusion doses (bolus 4 µg of NE or 50 µg of PE or infusion of 3.2 µg/minute and 4 µg/minute of NE or 40 µg/minute and 50 µg/minute of PE) have been tried (8-10) but the optimum dose is as yet not clearly known. Benefits in terms of increased CO and reduced incidence of bradycardia have also been demonstrated in these studies [7-10]. Hence, the present study was aimed to compare the efficacy and safety of prophylactic infusion of PE (50 µg/minute) and NE (5 µg/minute) for preventing hypotension during LSCS under SAB.

MATERIALS AND METHODS

This randomised clinical study was conducted in the Department of Anaesthesiology at a Tertiary Care Hospital, Vijaynagar Institute of Medical Sciences, Ballari, Karnataka, India. Study was done on the patients undergoing LSCS. The duration of the study was 12 months, from December 2018 to November 2019. Ethical clearance was obtained from Institutional Ethics Committee (VIMS/STD/PG/IEC/19/2019-20) and the study was registered with Clinical Trials Registry of India. (CTRI/2019/12/022505). Written consent was taken from the patients.

Inclusion criteria: A total of 156 parturients with singleton term pregnancy (primigravida and multigravida, American Society of Anesthesiologists (ASA) physical status II) scheduled for LSCS {Royal College of Obstetricians and Gynaecologists (RCOG) category 2 and below} under SAB were included in the study.

Exclusion criteria: Parturients at age outside the range of 18-35 years, height less than 150 cm or more than 180 cm, contraindications to SAB, allergy to drugs used in the study, eclampsia, preeclampsia, placenta previa, diabetes mellitus, hypertension, cardiovascular disease, contraindications to spinal anaesthesia and refusal to participate in the study by the subject, were the exclusion criteria.

Sample size calculation: In a preliminary study among 40 subjects, the incidence of hypotension was found to be 40% in group PE and 19% in group NE. The values were input to the online software, www.openepi.com {for 'Sample size: X-sectional, cohort, and Randomised Clinical Trials' (RCT)}. With two-sided significance level (1-alpha) of 95%, power (1-beta) of 80%, a sample size of 146 (73 in each group) were needed. The size was increased to 156 to compensate for losses, due to technical issues or patient refusals later/non cooperation, with 78 subjects in each group.

Study Procedure

The subjects were randomly allocated to one of the two study groups, group NE (n=80 parturients, to receive inj. NE) and group PE (n=80 parturients, to receive infusion of inj. PE) [Table/Fig-1], based on online randomisation software (https://www.randomizer.org). Allocation concealment was ensured using Sequentially Numbered Opaque Sealed Envelope (SNOSE) technique, with the envelopes being opened before implementing the randomisation case-wise. The subject was blinded to the group allocation; one investigator prepared the infusions and the rescue vasopressors and the second investigator, blinded to group allocation administered spinal anaesthesia and observed the patient intraoperatively and postoperatively.

Preoperative procedure: The possible adverse events to mother and child and the corrective measures were informed to all the subjects in detail in their own language and written consent was taken. Thorough preanaesthetic evaluation and necessary investigations were performed. All the patients received inj. ondansetron 4 mg and inj. pantoprazole 40 mg intravenous (i.v.), one hour before surgery. Fasting as per Indian Society of Anaesthesiologists (ISA) fasting guidelines was ensured. Subjects were transported to the operation theatre in left lateral position with an 18 G peripheral i.v. line over right forearm, for fluid and routine drug administration. After conducting preanaesthetic drill, the subjects were shifted inside the operation theatre. A second i.v. line was secured in the left/non dominant forearm for the administration of the test infusions. Non Invasive Blood Pressure (NIBP), pulse and Oxygen Saturation (SpO_2) by pulse oximeter and Electrocardiogram (ECG) monitoring were attached and basal values noted in supine position with left uterine displacement using 10 cm pillow under right buttock.

Subjects in group: The NE received 5 µg/minute of infusion of NE, prepared by diluting 1 mL of NE (=1 mg of the drug) with 9 mL Normal Saline (NS) to make a concentration of 100 µg/mL, out of which 5 mL was added to 100 mL of NS, to make a concentration of 5 µg/mL of infusion. Similarly, rescue boluses were prepared by serial dilutions to make a concentration of 5 µg/mL. Subjects in group PE received 50 µg/minute infusion of PE, prepared by diluting 1 mL of PE (=10 mg of the drug) with 9 mL of NS, to make a concentration of 1 mg/mL, out of which 5 mL was added to 100 mL NS to make a concentration of 50 µg/mL of infusion. Similarly, rescue boluses were prepared by serial dilutions to make a concentration of 50 µg/mL. Thus, the infusions were of same quantity and were maintained at same rate i.e., 1 mL/minute. The infusions were administered using BD Alaris™ GP Plus infusion pump via, the dedicated vein in non dominant forearm.

Intraoperative procedure: Under strict aseptic precautions, lumbar puncture was performed in left lateral position by a midline approach using 25 G Quincke spinal needle inserted in L4-L5 interspace and 9 mg (1.8 mL) of 0.5% bupivacaine (heavy) and 30 µg of fentanyl was administered sequentially. The subject was then turned supine with constant maintenance of left uterine displacement and drug infusions were started immediately to continue till end of the LSCS. Monitoring (BP, HR, ECG and SpO_2) was continued, recorded every three minutes till 30 minutes, later on every five minutes till 60 minutes and every 10 minutes later. Co-loading with 10 mL/kg of Ringer's Lactate was started in one i.v. line and the vasopressors were started just after SAB at the rate of 1 mL/kg, as per the group allocation in the other. Oxygen was delivered via Hudson's face mask at 6 L/minute. Sensory block level was assessed by pinprick with a 23 G hypodermic needle at midclavicular line bilaterally. If the level was higher than T4, the subject was excluded from the study. After delivery, 10 units of oxytocin was administered as infusion in 500 mL Ringer's Lactate, set for 30 minutes via infusion pump (rate adjusted if necessary). A decrease in systolic BP by 20% of baseline value was treated by administering a bolus dose of either 5 µg of NE or 50 µg of PE in group NE and group PE, respectively. Increase in the SBP by more than 20% of baseline value was first managed by stopping the respective prophylactic vasopressor infusion and monitored. Infusions were restarted when the SBP decreased to below the upper limit of the target range (20% above baseline). Atropine 0.6 mg was administered when sustained HR <50 Beats Per Minute (bpm) was observed (for one minute with decreasing trend), with maintained BP. For HR <60 bpm with maintained BP, the infusion was stopped. Increases in HR (>90 bpm-tachycardia) was also monitored. If the study drug infusion had to be stopped on three occasions, then the infusion was stopped henceforth, and BP was maintained with rescue boluses respective vasopressors for the remainder of the study.

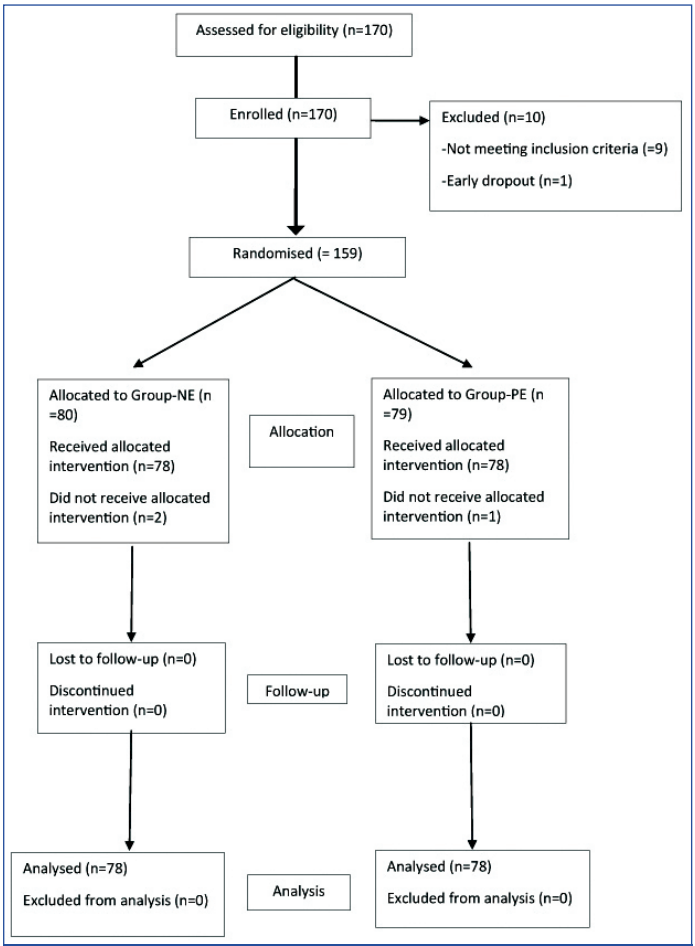
The primary outcome studied, was the incidence of hypotension in the two groups and the secondary outcomes included incidence of use of rescue bolus of vasopressors, the overall dose of vasopressors in those with and without hypotension, bradycardia, tachycardia, hypertension, number of additional interventions (drugs), nausea and vomiting and the Appearance, Pulse, Grimace, Activity and Respiration (APGAR) scores at one minute and five minutes. Overall number of interventions related to hypotension, bradycardia and hypertension were noted under physician interventions.

STATISTICAL ANALYSIS

Descriptive statistics for demographic and study parameters {mean±Standard Deviation (SD), Standard Error (SE), percentages/proportions, distribution for normalcy and ranges where necessary} were collected and entered in Microsoft excel 2010. After appropriate filtration, data was transferred and analysed by using software SPSS version 20.0. Based on normality of distribution, inferential statistical test were applied for intra and intergroup comparison for quantitative variables (Student's t-test, paired t-test and Wilcoxon signed-rank tests) and for qualitative variables (Chi-square, McNemar tests) among study groups. Tests for normalcy (goodness of fit) were conducted as necessary. The p-value <0.05 was considered to be statistically significant.

RESULTS

Among the 170 patients initially assessed for eligibility, 156 completed the study from recruitment to final analysis [Table/Fig-1]. There were no differences in the groups, in terms of the recruited patient characteristics [Table/Fig-2]. There was no difference in terms of the duration of the surgery [Table/Fig-3]. The incidence of hypotension was 17.9% in group NE and 26.8% in group PE, which was not statistically significant (p=0.182) [Table/Fig-4]. Rescue bolus vasopressor requirement was noted in 18% and 21% of patients, respectively in group NE and group PE [Table/Fig-4]. The infusion dose used (mean±SD) in group NE was 125.96±24.9 µg and in group PE, 1227.56±210 µg. The total doses (infusion and rescue bolus) were 190.55±36.20 µg and 2050.12±102.70 µg of NE and PE respectively, in the respective groups. In those developing hypotension, the bolus doses used were noradrenaline 70.30±14.54 µg and PE 1050.58±217.00 µg, respectively and the total doses (bolus+infusion) were 218.01±43.84 µg and 2344.12±310.76 µg, respectively. The total dose in patients not developing hypotension (only infusion, no bolus) was 158.29±30.10 µg and 1495.47±68.52 µg in NE and group PE, respectively. The trend of Systolic Blood Pressures (SBP) (mean) and HR (mean) with management (as per groups) intraoperatively is shown in [Table/Fig-5,6]. The trend of changes in SBP was similar in both groups but incidence of hypotension was more in the group PE, especially between 5th to 20th minute after spinal anaesthesia. The HR was maintained at lower level in group PE as compared to group NE, especially between 5th to 30th minute. The incidence of bradycardia was higher in group PE [Table/Fig-4]. The overall number of physician interventions was not different between the groups [Table/Fig-4]. The basal Diastolic Blood Pressure (DBP) (p-value=0.92) and the changes over time did not differ significantly between the groups. There were minimal falls till 10 minutes in both the groups (p-value=0.27) and were also similar at 60 minutes (p-value=0.20). [Table/Fig-4]. The SpO_2 was uniformly between 99% to 100% in both groups with O_2 supplementation by mask. The ECG monitoring did not show any non sinus events or other abnormalities in both groups.



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) flowchart for the study.

Parameters	Group (n)	Mean±SD	p-value*
Age (in years)	NE (78) PE (78)	24.47±2.52 23.91±2.63	0.173
Weight (Kg)	NE (78) PE (78)	59.41±5.99 60.09±5.44	0.459
Height (cm)	NE (78) PE (78)	153.35±2.74 152.14±2.16	0.312
BMI (kg/m^2)	NE (78) PE (78)	25.20±2.34 25.90±2.32	0.124

[Table/Fig-2]: Patient demographics.
NE: Norepinephrine; PE: Phenylephrine (*Student's t-test)

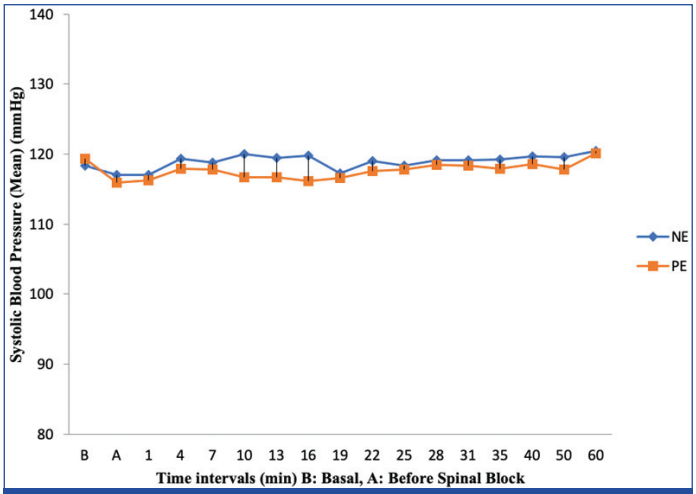
Duration (in minutes)	NE (n=78)	PE (n=78)	Total (N=156)	p-value
20-25	56	60	116	0.242
25-30	9	7	16	
30-35	7	9	16	
35-40	3	1	4	
40-45	2	1	3	
>45	1	0	1	
Mean	25.19±3.90	24.5±2.85	156	

[Table/Fig-3]: Duration of surgery in the two groups.
NE: Norepinephrine; PE: Phenylephrine

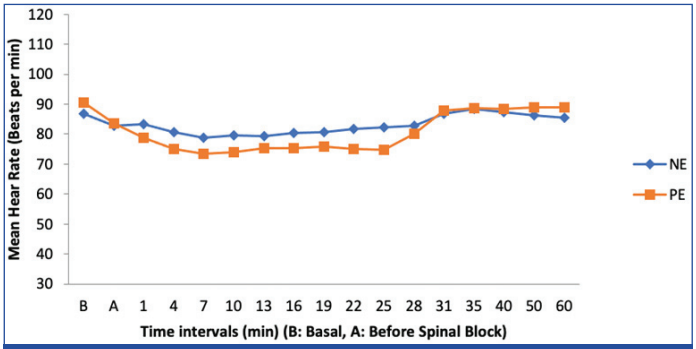
Parameters		NE (n=78)	PE (n=78)	p-value
Incidence of hypotension, n (%)		14 (17.9)	21 (26.8)	0.182
Total infusion dose of vasopressor used (µg) (Mean±SD)		125.96±24.9	1227.56±210	0.147*
Number of patients needing rescue bolus vasopressor, n (%)		14 (17.9)	16 (20.5)	0.340
Bolus rescue vasopressor dose in patients developing hypotension (µg) (Mean±SD)		70±14.54	1050±217.00	0.181*
Total dose (infusion+rescue) in patients developing hypotension (µg) (Mean±SD)		218.01±43.84	2344.12±310.76	0.240*
Total dose (infusion, no bolus) in patients not developing hypotension (µg) (Mean±SD)		158.29±30.10	1495.47±68.52	0.316*
Total amount of vasopressor used (µg) -infusion plus bolus) in all patients (Mean±SD)		190.55±36.20	2050.12±102.70	0.152*
Diastolic blood pressure changes (mmHg) (Mean±SD)	Basal	73.50±9.18	73.37±8.28	0.92
	10th min	72.60±10.62	70.67±9.95	0.27
	60th min	72.20±8.49	70.85±3.98	0.20
Incidence of bradycardia, n (%)		3 (3.8)	17 (21.8)	0.053
Number of patients needing atropine		0	5 (6.4)	0.162
Incidence of hypertension		10 (12.8)	6 (7.6)	0.290
Incidence of tachycardia		5 (6.4)	2 (2.6)	0.241
Overall number of physician interventions		24	27	0.154

[Table/Fig-4]: Haemodynamic changes and drug interventions in the two groups.
NE: Norepinephrine; PE: Phenylephrine; *PS: All vasopressor comparisons based on fixed proportional dosages of two drugs

Majority of the neonates (66/78 and 65/78 in groups NE and PE, respectively) had APGAR scores of more than eight at 1st minute and by 5th minute, 90% of the neonates had scores above eight (p-value=0.16). One neonate had score <6 at five minutes in group NE and none in group PE.



[Table/Fig-5]: Systolic blood pressure (mean) in two groups at different time intervals.



[Table/Fig-6]: Heart rate (mean) in two groups at different time intervals.

DISCUSSION

The incidence of hypotension after prophylactic i.v. infusion of either NE or PE at 5 µg/minute and 50 µg/minute, respectively was statistically similar in the two groups of parturients receiving spinal anaesthesia. The infusion doses, the number of patients needing the rescue doses were also similar in the two groups. The total dose (infusion and rescue bolus) were also not significantly different between the groups [Table/Fig-4]. NE infusion was found to be associated with lesser incidence of bradycardia compared to PE infusion, but the number of subjects needing atropine was similar in the two groups. The spinal anaesthesia induced hypotension is because of the reduction in Systemic Vascular Resistance (SVR) with secondary increases in HR and CO. PE is the popular agent for correction of this hypotension and acts by increasing the SVR due to α-adrenergic effects [2]. However, there is a tendency for dose related fall in the CO, due to fall in the HR, even with slight increases of BP [7]. This disadvantage has been sought to be avoided by the use of noradrenaline, which has slight β-adrenergic effect, apart from the signature α-agonism, with overall neutral effect on HR but with increase in CO. The uteroplacental circulation is hence, expected to be better with noradrenaline. Also, in parturients, when bradycardia accompanies hypotension, noradrenaline would be a better choice than PE [2]. Incidence of maternal hypertension, tachycardia and the neonatal APGAR scores, at 1st and 5th minute after foetal extraction were also comparable. Only one neonate, with a low birth weight had score < 6 at five minutes and was monitored and managed in the neonatal unit of the hospital. The authors did not take the blood sample of the umbilical cord but in a study at 5 µg/mL and 100 µg/mL infusions of NE and PE [7] (dilution of PE was double that of current study), there were lower umbilical plasma catecholamine concentrations together with greater umbilical vein pH and oxygen content in the group NE. This may be due to decreased foetal stress in noradrenali group NE when compared with the group PE, with greater uteroplacental oxygen delivery of the latter.

The doses of NE and PE were studied in an old research [11] and based on that, preparations of 5 µg/mL of NE and 100 µg/mL of PE were used, with infusions at 0-5 µg/minute and 0-100 µg/minute in a computer controlled infusion study by Ngan Kee WD et al., [7]. They surmised, from the results of their study, that even though, the results favoured use of NE, the median infusion rate required to maintain BP was greater in the group NE. Thus, the effective ratio of two drugs could be less than 1:20. The present and other studies used this graded approach to adjust and calculate the dose of the drugs [12]. Another study compared prophylaxis at 25, 50, 75 and 100 µg/minute infusions of PE for prevention of hypotension after caesarean section under spinal anaesthesia and concluded that, 50 µg/minute dose provided stable haemodynamics and good neonatal outcome [13]. Bolus doses of 8 µg NE and 100 µg of PE were compared in another study in parturients undergoing emergency caesarean section for foetal compromise under spinal anaesthesia [14]. There were no significant differences in the neonatal outcomes (primary outcome) and in the haemodynamics between the two groups. Hence, the authors decided to use fixed lower dose infusion of PE, at 50 µg/minute and compare with 5 µg/minute of NE infusion), contributing to practical background effect, and then calculate the total doses required considering the supplemental doses as well.

Ngan Kee WD et al., tried the use of NE as vasopressor in obstetric practice for the first time [7]. NE 5 µg/mL or PE 100 µg/mL were used with a computer-controlled infusion to maintain SBP in 104 healthy parturients undergoing CS under spinal anaesthesia with hyperbaric bupivacaine 0.5% (2.2 mL) and fentanyl,15 µg. After co-hydration with Ringer's Lactate (RL), the drug infusions were started and adjusted limits of 0 to 60 mL/hour (0-5 µg/minute of NE or 0-100 µg/minute of PE) based on computer-controlled closed-loop feedback system. Normalised CO at five minutes (primary outcome) was greater in the group NE compared with that in the group PE and from induction until uterine incision, for NE versus PE, SBP and stroke volume were similar, HR and CO were greater, SVR was lower, and the incidence of bradycardia was lesser. Neonatal outcome was similar between groups. Subsequent studies used different dose ranges; Hasanin A et al., in a study in full term singleton pregnant women, 18-40 years and posted for elective LSCS used 0.05 µg/kg/minute and 0.75 µg/kg/minute infusions of NE and PE prophylactically [15]. Hyperbaric bupivacaine 10 mg with 20 µg fentanyl and co-loading with RL was carried out. Hypotension (SBP ≤80% of the baseline reading) was managed by increasing the vasopressor infusion rate by 20% in addition to a vasopressor bolus. The incidence of post-spinal hypotension was comparable in both the groups. Reactive hypertension was reduced by 50% and so was the incidence of bradycardia in group NE, as compared to group PE. Group NE showed lower number of physician interventions per mother compared to group PE. The neonatal outcomes (APGAR scores and umbilical blood gases) were comparable between the groups. The overall number of 'physician interventions' in the present study (hypotension, hypertension and bradycardia related) were comparable in the two groups.

The various published evidences on the use of NE and PE for either therapeutic or prophylactic purposes, the doses as infusions or boluses, the rescue boluses, their Patient/population, Intervention, Comparison and Outcomes (PICO) characteristics are shown in [Table/Fig-7] [7-10,12,14-17]. Vallejo MC et al., conducted a study on 85 singleton pregnant women, more than 36 weeks of gestation belonging to ASA <3, who were randomised to one of the two treatment groups (group PE- 100 µg/mL infused at 0.1 µg/kg/minute or Group N: NE infused at 0.05 µg/kg/minute, to receive PE or NE) to maintain SBP within 100%-120% of baseline during standardised spinal anaesthesia [16]. The requirements of rescue bolus were higher in group PE (65.8%) than group NE (48.8%)

S. No.	Studies	Place of study	Population studied	Study drugs usage/dose/ dilution	Parameters assessed as per the present study	Other parameters	Conclusion
1	Ngan Kee WD et al., 2015 [7]	Hong Kong	Singleton, term pregnancy, elective CS	Prophylactic. Computer-controlled infusion of NE 5 µg/mL or PE 100 µg/mL	BP, HR, neonatal outcome	CO	NE maintained BP, with greater HR, CO
2	Mohta M et al., 2019 [14]	Delhi	Singleton, elective CS	Therapeutic. 100 µg PE and 5 µg NE boluses for treatment of postspinal hypotension	Incidence of maternal bradycardia No. of hypotensive episodes, No. of boluses required to treat the first hypotensive episode or reactive hypertension	-	Both NE and PE reversed hypotension without statistically significant difference in maternal bradycardia. Umbilical artery pH higher after PE
3	Vallejo MC et al., 2017 [16]	United States of America	Singleton, >36 weeks' gestation, ASA <III, elective CS	Prophylactic. PE 100 µg/mL infused at 0.1 µg/kg/minute or NE infused at 0.05 µg/kg/minute) to maintain SBP within 100 120% of baseline. Bolus doses for hypotension	SBP, DBP, HR, type of provider interventions for maintaining BP, APGAR scores <7 at 1st and 5th minute	CO, CI, stroke volume, etc., umbilical cord blood gases	NE fixed-rate infusion can be an alternative to PE
4	Hasanin A et al., 2019 [15]	Cairo, Egypt	Full term singleton for elective CS	Prophylactic. 0.05 µg /kg/minute NE and 0.75 µg/kg/minute PE, then manually adjusted for maintaining BP along with bolus	Incidence of postspinal hypotension, severe hypotension, APGAR	Umbilical blood gas analysis	NE more effective in maintaining SBP, Lower number of physician interventions, reactive hypertension, bradycardia
5	Puthenveettil N et al., 2019 [8]	Kochi, India	Singleton pregnancy, ASA II, elective CS	Therapeutic. PE 50 µg or NE 4 µg bolus	No. of bolus doses of NE/PE required to treat hypotension. Incidence of bradycardia, hypertension and foetal outcomes	-	Intermittent boluses of NE effective. The neonatal outcomes were similar in both the groups. NE boluses can be considered as alternative to PE boluses
6	Theodoraki K et al., 2020 [10]	Athens, Greece	Elective CS, ASA<i.v.	Prophylactic. Start, fixed rate: NE at 4 µg/ minute or PE at 50 µg/minute. Maintain with bolus NE or PE based on hypotension and HR	Maternal HR, BP, and neonatal outcomes	Change in CI by thoracic bioreactance from SA to umbilical cord clamping, Fluids administered, umbilical vein blood gases	NE associated with lower tendency for bradycardia, bradycardia related interventions. Similar BP and HR maintenance, maternal foetal outcomes
7	Goel K et al., 2021 [12]	Ludhiana, India	ASA II/III for elective CS	Prophylactic. Variable rate, manually controlled infusions of PE and NE targeting maintenance of SBP to 100% of baseline	Maternal haemodynamics, episodes of hypotension, vasopressor consumption	-	Dilute solution of NE infusion comparably efficacious to the current gold standard vasopressor PE in maintaining BP
8	Chen Z et al., 2022 [9]	Chengdu, China	Twin gestation, elective CS	Prophylactic. Infusions of NE 3.2 µg/minute or PE 40 µg/minute bolus if SBP <90 mmHg or 80% of baseline - NE 8 µg or PE 100 µg	Change of HR and BP. Maternal complications, neonatal outcomes, APGAR scores	Umbilical blood gas status	No significant difference in HR. SBP significantly lower with NE but physician intervention no significant difference
9	Belin O et al., 2023 [17]	Orleans, France	Elective CS	Prophylactic. NE starting rate of 0.05 µg/ kg/minute or PE at 0.5 µg/kg/ minute Then, manually adjusted to maintain SBP >90% basal	Maternal BP, neonatal outcomes	Change in Cardiac Index (CI) by thoracic bioreactance	In group NE, CI better maintained compared to group PE. Neonatal hypoglycaemia more common in group PE. Both agents effective in maintaining BP
10	Present study	Ballari, India	Primipara/multipara, singleton, ASA II, category 2 and below	Prophylactic. NE 5 µg/minute or PE 50 µg/minute, rescue bolus of respective drugs	Incidence of hypotension, total doses of test drugs, bradycardia, hypertension, tachycardia, neonatal status (APGAR), etc	-	Incidence of hypotension after NE and PE- not statistically different. Incidence of bradycardia, more with PE

[Table/Fig-7]: Comparative studies in CS under spinal anaesthesia with prophylactic/therapeutic norepinephrine and phenylephrine [7-10,12,14-17].
CS: Cesarean section; ASA: Anaesthesiologists; NE: Norepinephrine; PE: Phenylephrine; SBP: Systolic blood pressure; BP: Blood pressure; HR: Heart rate; DBP: Diastolic blood pressure; APGAR: Appearance, pulse, grimace, activity and respiration; CO: Cardiac output; CI: Cardiac index; SA: Spinal anaesthesia

but without any statistical significance. There were no differences between groups in the proportion of APGAR scores <7 at one minute and five minutes, or in umbilical venous cord blood gases. One patient in group PE and two in group NE required infusion cessation because of hypertension; only one of them in group PE became bradycardic. The authors used the fixed rates of infusions similar to the present study.

In a randomised controlled trial of 124 parturients posted for elective CS under spinal anaesthesia, either NE (at 0.05 µg/kg/ minute) or PE (at 0.5 µg/kg/minute) were started and the infusion was then adjusted manually, to target and maintain maternal systolic BP above 90% of the baseline value [17]. The primary outcome was the change in Cardiac Index (CI) measured from time of SAB to umbilical cord clamping measured by thoracic bioreactance. NE use was associated with better CI (maintained between 90% and 100% of baseline). Maternal blood pressure maintenance and neonatal outcomes were comparable, but severe neonatal hypoglycaemia was more common in group PE. On the maternal side, NE could stimulate increase in glucose metabolism and decrease in the β-receptor-mediated insulin release. This results in higher maternal blood glucose level at the time of umbilical cord clamping, transplacental glucose transfer and increased neonatal glucose [14]. Based on the present study and many other studies with different dosing for infusion, it is clear that, the equipotent ratio of NE and PE needs to be refixed [7,12-14]. In the current study, the infusion had to be stopped in 23% of parturients in group NE and

12.8% in group PE due to reactive hypertension; the infusion was restarted after the SBP came back to within normal limits. The results of the present study will help in streamlining the dose and use the vasopressors judiciously in future, with potential for use in complicated obstetrics as well.

Limitation(s)

Evidences using CO monitoring as outcome measure have so far attested to the positive benefit of NE in terms of improved CO and not much in terms of maintenance. This way, the current study had limitations, as this parameter was not monitored. Neonatal status with umbilical cord blood and assessment of neonatal glucose levels also would have added value to the study.

CONCLUSION(S)

Noradrenaline has a great potential for prophylactic use against hypotension after spinal anaesthesia for LSCS as the maternal CO and HR are better maintained, as compared to PE with better foetal profile as well. At infusion doses of 5 µg/minute and 50 µg/minute of NE and PE respectively, the incidence of hypotension after prophylactic infusions of either drugs after spinal anaesthesia for LSCS was not statistically different. Incidence of bradycardia was more with PE, with risk of fall in CO. Thus, NE infusion at 5 µg/minute may be potentially beneficial in obstetric patients.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Apr 06, 2023
- Manual Googling: Apr 27, 2023
- iThenticate Software: May 24, 2023 (16%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Apr 04, 2023**
Date of Peer Review: **Apr 27, 2023**
Date of Acceptance: **May 26, 2023**
Date of Publishing: **Jul 01, 2023**