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Original Research Article

Comparison of Norepinephrine and Phenylephrine Boluses for the Treatment of Hypotension during Spinal Anaesthesia for Caesarean Section

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Abstract

Background and Aims: Hypotension is common despite adequate fluid loading following spinal anaesthesia for caesarean section. Phenylephrine is presently the drug of choice to treat spinal hypotension following caesarean section. Recently, norepinephrine is being proposed as a substitute to phenylephrine boluses. The aim of the study was to compare the effectiveness of bolus doses of norepinephrine with phenylephrine to treat hypotension following spinal anesthesia for caesarean section.

Methods: 100 patients undergoing elective caesarean section under spinal anaesthesia were randomly assigned into two groups. Group PE patients received phenylephrine 50 µg as an IV bolus and group NE received 4 µg of norepinephrine as IV bolus to treat hypotension following spinal anesthesia. The primary objective of the study was to compare the number of bolus doses of norepinephrine or phenylephrine needed to treat hypotension following spinal anesthesia. The secondary objectives were to compare the incidence of bradycardia, nausea and vomiting in mother and foetal outcomes.

Results: The number of boluses of vasopressors required to treat hypotension was significantly lower in group NE (Group NE=1.36±0.563, Group PE=2.00±0.699, p-value=0.000). The frequency of bradycardia was high in group PE, and this difference was also statistically significant (Group NE=2 (4%), Group PE=11 (22%) p-value=0.015). Maternal complications such as nausea and vomiting and shivering were comparable between the groups. The fetal parameters were also comparable between both the groups.

Conclusion: Intermittent boluses of norepinephrine are effective in the management of hypotension following spinal anesthesia for caesarean section. The fetal outcomes were comparable in both the groups. Norepinephrine boluses can be considered as a better alternative to phenylephrine boluses.

Keywords: Caesarean section, spinal anesthesia hypotension, norepinephrine, phenylephrine.

Introduction

The most popular choice of anesthesia for caesarean section is subarachnoid block which is attributable to its quick onset of action, excellent surgical anesthesia, wholesome patient comfort and lesser incidence of complications.[1] However, spinal anesthesia is not totally risk-free as it is associated with significant hemodynamic changes. The common side effects of spinal anaesthesia are maternal hypotension, which causes vomiting, nausea, decreased uteroplacental blood flow and an increased risk of foetal acidosis.[2] Hypotension is common in women who receive sub-arachnoid block for Caesarean delivery, with an incidence of up to 71%.[2] The decrease in systolic blood pressure impairs uterine blood flow and fetal circulation, which results in hypoxia and acidosis in the fetus.[3] Treatment of spinal induced hypotension includes, patient positioning preventing aorto-caval compression by gravid uterus and increasing intra-vascular volume using crystalloids and colloid.[4,5] However, the mainstay of treatment for spinal anaesthesia-induced hypotension is intravenous vasopressors.[6,7] phenylephrine the current drug of choice in preventing and treating spinal anesthesia induced hypotension.[8] Phenylephrine is a potent

vasopressor with rapid onset and short duration of action. However, it causes reflex bradycardia which leads to decreased cardiac output, which my lead to adverse fetal and maternal outcome. Noradrenaline, another potent vasopressor, an alpha -1 and beta -1 agonist and is mainly used in critical care setting. It causes reflex negative chronotropic action due to its potent alpha agonist effect, which is balanced by the weak beta agonist mediated positive chronotropic effect.[9] Hence it has a lesser tendency to cause bradycardia as compared to phenylephrine. Phenylephrine 100 µg is equipotent to 8 µg norepinephrine.[10] The aim of the study was to compare the bolus doses of norepinephrine with phenylephrine in treating spinal hypotension during caesarean section under spinal anesthesia.

Materials and Methods

This prospective double-blinded randomised control trial was conducted in a tertiary care teaching hospital after approval from the hospital ethics committee (067-2022/I-S-T/43/Dt.17.05.22), Clinical Trial Registry of India (CTRI) registration (CTRI/2022/11/047015) and written informed consent from patients between November 2022 and February 2023. The study was conducted as per consort guidelines and followed ethical guidelines of the Declaration of Helsinki. Hundred term parturients between 21 and 35 years of age with singleton pregnancy belonging to the American Society of Anesthesiologists (ASA) physical class II posted for elective caesarean section under spinal anaesthesia were included in the study. Parturients with allergy or hypersensitivity to phenylephrine or norepinephrine, height <140 or >180 cm, any hypertensive disorders of pregnancy, cerebrovascular or cardiovascular disease and foetal abnormalities were excluded from the study. All patients were premedicated with oral metoclopramide 10 mg and ranitidine 150 mg on the night prior to surgery. In the operation theatre, 18-gauge intravenous cannula was inserted, and standard monitoring with non-invasive blood pressure, electrocardiography and pulse oximetry was established. The baseline vitals were noted. They were then loaded with 15 mL/kg of lactated Ringer's solution. Subarachnoid block (at L3–L4 or L4–L5 level using standard technique) with 2 mL of 0.5% hyperbaric bupivacaine was given using 25-G Quincke's spinal needle in the left or right lateral position. The patients were then turned supine with a wedge under the right buttock.

The highest level of sensory blockade achieved was assessed 5 min after intrathecal injection. The parturients were randomised into group PE and NE by computer-generated random sequence of numbers and concealed by closed envelope technique. The anaesthetist posted in the post anesthesia care unit prepared the drugs. Norepinephrine and phenylephrine were prepared in an identical coded 10-mL syringe to give norepinephrine 4 µg/mL (Noracare, Arvincare) and phenylephrine 50 µg/mL (Phenpres LS, Neon). The anaesthetist in the OT used vasopressor-labelled syringe to treat hypotension (systolic blood pressure dropped below 20% of baseline) and collected the data in preformed pro forma for analysis. The patient and the investigator both were blinded. Blood pressure and heart rate were monitored every 2 min till 10 min, and every 5 min till the end of surgery. Group PE patients were given phenylephrine 50µg as an IV bolus and group NE patients were given 4µg of norepinephrine IV bolus to treat hypotension. After the baby is delivered, 10 U of oxytocin slow infusion was given. Incidences of hypotension, bradycardia and the no. of boluses of vasopressors used intraoperatively were noted. Bradycardia was defined as heart rate less than 50 beats/min (bpm) and was treated with intravenous atropine 0.6 mg.

A paediatrician who was unaware of the vasopressor used noted Apgar score at 1-min and 5-min. Umbilical vein sample at the time of birth for blood gas analysis was collected, and pH, PCO2 and bicarbonate were analysed. The total duration of surgery was noted. Incidences of nausea or vomiting due to maternal hypotension were also noted. The primary objective of the study was to compare the number of IV bolus doses of norepinephrine or phenylephrine required to treat hypotension in parturients to treat hypotension due to spinal. The secondary objectives were to compare the incidence of bradycardia, nausea and vomiting in mother and foetal outcomes such as Apgar score and umbilical vein blood gases. As per article, "Comparison of norepinephrine and phenylephrine boluses for the treatment of hypotension during spinal anaesthesia for caesarean section – A randomised controlled trial"[11] the number of boluses of vasopressors required to treat hypotension in group of patients receiving Norepinephrine is 1.40 ± 0.577 vs. the number of boluses of vasopressors required to treat hypotension in group of patients receiving Phenylephrine is 2.28 ± 1.061, and with 95% confidence and 80% power, minimum sample size was calculated to be 23 in each group (total 46). We included 100 participants in our study (50 in each group). All the statistical analysis was done in IBM SPSS 23.0 (SPSS Inc, Chicago, USA). The results are given as mean ± standard deviation for all the continuous variables and frequency for categorical variables. Pearson's Chi-square test with continuity correction was used for finding the association between two categorical variables. Independent sample t-test was applied for comparing the mean of continuous parameters between two groups. Paired sample t-test was used to compare the average Apgar score at 1 and 5 min within the groups. P value of <0.05 was considered as statistically significant difference.

Results

The study included 100 patients who were randomly allocated into two equal groups [Figure 1]. The patient demographics with respect to age, height, weight, and ASA physical status were comparable between the two groups. All patients achieved adequate spinal block height above T5 at 5 min, and the level of dermatomal height achieved was comparable between the groups. The surgical times required were also comparable between the groups [Table 1, 2]. The number of boluses of vasopressors required to treat hypotension was significantly lower in group NE patients (Group NE=1.36±0.563, Group PE=2.00±0.699, p-value=0.000).

The frequency of bradycardia was high in group PE, and the difference was statistically significant [Group NE=2 (4%), Group PE=11 (22%) p-value=0.015] [Table 3]. Maternal complications such as nausea, vomiting and shivering were comparable between the groups. The foetal parameters were comparable between the two groups, and no statistical difference was noted [Table 4].

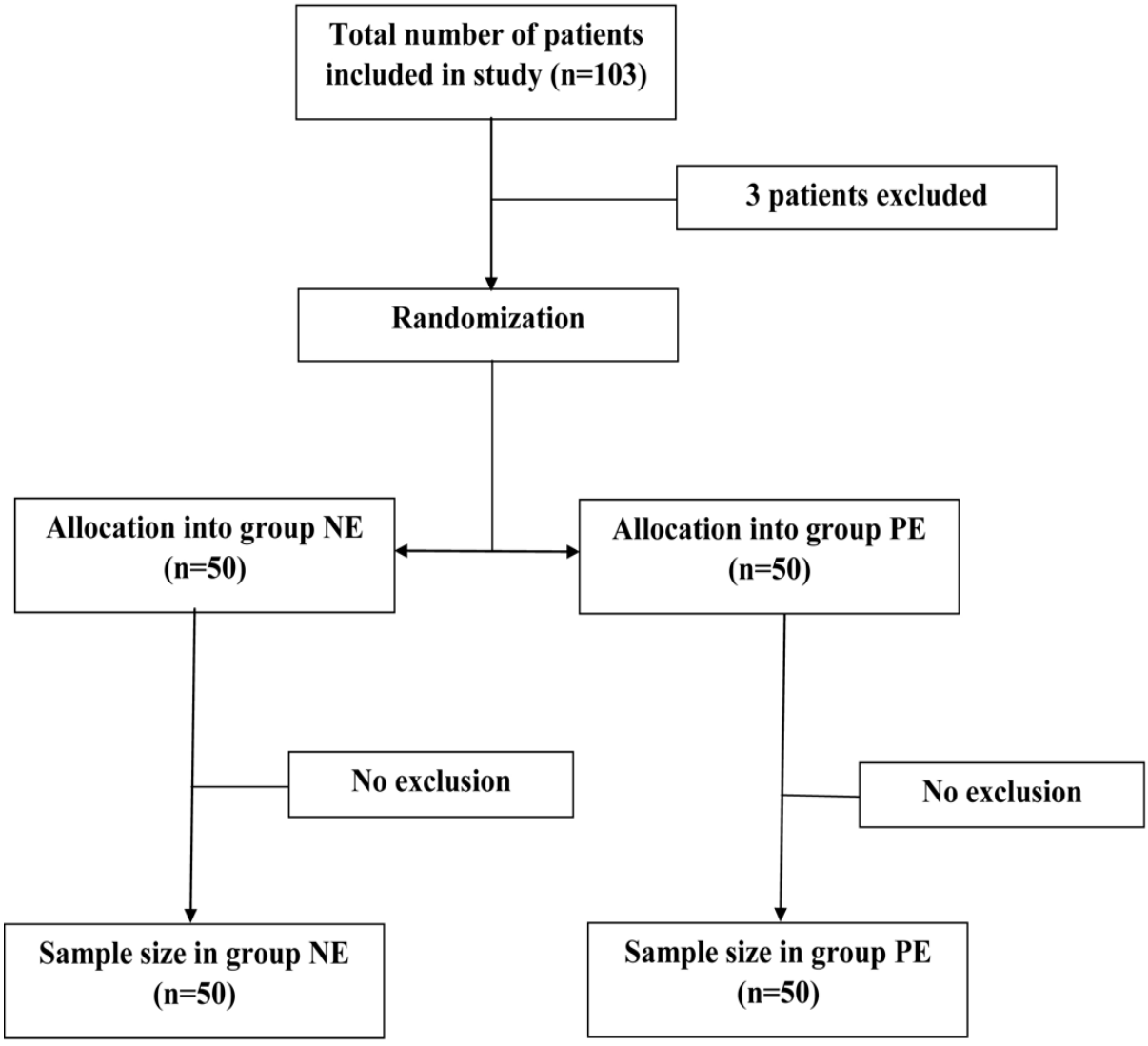

Figure 1: Consort flow diagram

Table 1: Comparison of demographic profile

Demography	Group NE (n=50)	Group PE (n=50)	P Value
Age (years)	26.08±3.288	25.94±3.616	0.840 (NS)
Weight (kg)	71.98±6.046	73.14±6.389	0.353 (NS)
Height (cm)	149.30±4.249	147.96±4.257	0.118 (NS)

*NS= non-significant

Table 2: Comparison of Duration of surgery and block height

	Group NE (n=50)	Group PE(n=50)	P Value
Duration (min)	58.86±3.891	60.2±4.136	0.098(NS)
Block Height			
T3	2	0	0.304(NS)
T4	26	30	
T5	22	20	

*NS= non-significant

Table 3: Comparison of Haemodynamic variables

	Group NE (n=50)	Group PE (n=50)	p-value
No. of boluses of vasopressors	1.36±0.563	2.00±0.699	0.000(S)
Incidence of bradycardia	2 (4%)	11 (22%)	0.015(S)

Table 4: Comparison of Maternal and Fetal parameters

	Group NE (n=50)	Group PE (n=50)	p-value
Maternal shivering	6 (12%)	6 (12%)	1.000
Maternal nausea and vomiting	4 (8%)	4 (8%)	1.000
pH of cord blood	7.327±0.312	7.323±0.310	0.533
pO2	34.96±7.753	35.74±5.915	0.578
pCO2	43.50±2.643	42.88±2.666	0.246
Lactates	1.986±0.140	1.982±0.1034	0.860
APGAR SCORE	APGAR at 1 min		
7	8 (16%)	11 (22%)	0.724
8	14 (28%)	12 (24%)	
9	28 (56%)	27 (54%)	
APGAR at 5 min			
8	2 (4%)	0 (0%)	0.353
9	24 (48%)	24 (48%)	
10	24 (48%)	26 (52%)	

Discussion

In our study we found out that the number of boluses of vasopressors required to treat hypotension was significantly lower in group NE patients. (Group NE=1.36±0.563, Group PE=2.00±0.699, p-value=0.000) and the frequency of bradycardia was high in group PE, and the difference was statistically significant [Group NE=2 (4%), Group PE=11 (22%) p-value=0.015].

In a similar randomised double blinded controlled trial conducted by Hasanin et al [12], 140 mothers were screened for eligibility, which aimed to compare the efficacy and safety of PE and norepinephrine when used in variable infusion rate during caesarean delivery, participants were given prophylactic vasopressors after spinal anesthesia at rate started at 0.05 microgram/kilogram/minute (phenylephrine) and 0.75 microgram/kg/minute respectively. Although the incidence of bradycardia was almost halved in NE group compared to PE group these differences did not reach statistical significance (P =value of 0.1). We found similar result in our study, with incidence of bradycardia of 4 % in group NE compared to 22 % in group PE with p-value of 0.015, making the result statistically significant.

Similarly, a double-blind randomised controlled trial by M Mohta et al [9], a total of 90 women were included and allocated into two groups, the phenylephrine group and norepinephrine group. The participants received 100mcg phenylephrine (n=58) and 5 mcg noradrenaline (n=61) as boluses. The incidence of bradycardia was 37.8% with phenylephrine as compared to 22.2% with noradrenaline group (p value was 0.167), which was not statistically significant.[9] We also found similar results in our study, but it was statistically significant (Group NE 4% vs Group PE 22%, p-value 0.015).

Similarly, a randomised double-blind study conducted by Goel et al. [13] on 200 parturient undergoing caesarean section under subarachnoid block (SAB) were randomised to two groups, A-phenylephrine group (n=102) and B-norepinephrine group (n=102) to receive variable rate, manually controlled infusions of phenylephrine and norepinephrine targeting maintenance of SBP to 100% of the baseline value. The infusion rate of phenylephrine was kept within the limits of 0 to 60 mL/h [0–100 mcg/min] and that of norepinephrine within 0 to 60 mL/h [0–5 mcg/min]. Similar to our study the incidence of bradycardia was higher in group A (phenylephrine) than in group B (noradrenaline) which was statistically significant

(16% versus 1% respectively; P value- 0.001). The higher episodes of bradycardia observed in group A (phenylephrine) were due to the result of its α-adrenergic agonist properties which leads to decrease heart rate (HR) and cardiac output (CO), occurring even when BP is maintained at baseline. Norepinephrine group had a lesser reduction in HR due to its both direct positive chronotropic along with the reflex negative chronotropic actions. This study stated that diluted solution of norepinephrine infusion is comparably efficacious to the current gold standard vasopressor phenylephrine in maintaining blood pressure following spinal anaesthesia for caesarean delivery, with a significantly lower incidence of bradycardia.

In a similar study by NganKee et al. [14] which enrolled 668 subjects having elective and non-elective caesarean delivery under spinal or combined spinal epidural anaesthesia in randomised, double-blind, two-arm parallel, non-inferiority clinical trial, participants received norepinephrine 6mcg/ml and phenylephrine 100mcg/ml either prophylactically, either as an infusion or bolus. Similar to our study, incidence of bradycardia was lower in the norepinephrine group (26%) as compared to the phenylephrine group (42%) (RR=0.61; 95% CI, 0.49-0.77).

In a study conducted by Puthenveettil et al [11], fifty patients undergoing elective caesarean section under spinal anaesthesia were randomly assigned into two groups. Group P patients received phenylephrine 50 micrograms as an IV bolus and group N received 4 micrograms of norepinephrine as IV bolus to treat post-spinal hypotension.

Similar to our study, in this study also the number of boluses of vasopressors required to treat hypotension was significantly lower in group N patients compared to P group (1.40 ± 0.577 vs. 2.28 ± 1.061, P = 0.001). Puthenveettil et al. also found that the frequency of bradycardia was high in group P, but the difference was not statistically significant (4% vs. 20% P = 0.192); in our study the frequency of bradycardia was also high in group PE, but the difference was statistically significant unlike the mentioned study [Group NE=2 (4%), Group PE=11 (22%) p-value=0.015]. Similar to our study, the foetal parameters were comparable between the two groups, and no statistical difference was noted and maternal complications such as nausea, vomiting and shivering were also comparable between the groups.

In our study, the incidence of nausea and vomiting was 8% in both Group NE and Group PE and was comparable. There are controversies regarding the use of norepinephrine through peripheral veins, but we did not encounter side effects with its use in any of our patients.The major limitation of the present study was that we used vasopressor to maintain the systolic pressure without monitoring the cardiac output. We could have used non-invasive cardiac output monitor. Furthermore, a larger sample size could have provided a wider perspective on maternal and foetal effects.

The study can be extended to a larger number of patients with intermittent or continuous infusions of norepinephrine.

Conclusion

In this prospective Double-Blind Randomized controlled study, comparing the bolus doses of norepinephrine versus phenylephrine for the management of maternal hypotension during caesarean delivery under spinal anesthesia, we found that intermittent boluses of norepinephrine are statistically significant in effectively maintaining the haemodynamic parameters better as compared to boluses of phenylephrine following spinal anesthesia during caesarean section.

There was no significant difference in complications among both the groups and the neonatal arterial blood gases and Apgar scores are also comparable with phenylephrine.

Thus, we conclude that norepinephrine boluses can be considered as a better alternative to phenylephrine boluses for the management of spinal-induced hypotension during caesarean section.

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