

A Comparative Study to Evaluate Phenylephrine and Norepinephrine Boluses for the Treatment of Post Spinal Hypotension during Elective Caesarean Section

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Abstract

Background: Phenylephrine is the first-line choice for prevention and treatment of hypotension during spinal anaesthesia for caesarean section. In a quest for new drug, we compared norepinephrine with phenylephrine boluses to treat hypotension following spinal anaesthesia during caesarean section.

Materials and Methods: After obtaining institutional ethics committee clearance (Reference No:EC138), CTRI/2022/08/044705, informed consent was taken, and the study was conducted on 60 patients of 20-35years age group. Patients were randomized in to two groups of 30 each. Group N received norepinephrine (6 mcg) and Group P receives phenylephrine (100 mcg) to treat hypotension following spinal anaesthesia. The primary outcome was to compare number of boluses of each vasopressor required to treat hypotension following spinal anaesthesia. The secondary outcome was to compare APGAR score in the newborn.

Results: 27 mothers in phenylephrine group and 28 mothers in norepinephrine group developed hypotensive episodes. In Phenylephrine group, mean number of vasopressor boluses needed were 1.185 ± 0.388 and in Norepinephrine group they were 1.107 ± 0.309 with p value 0.3926. The Number of boluses of vasopressor required to treat hypotension was lower in Norepinephrine group when compared to phenylephrine group. There was no statistically significant difference in Number of Vasopressor Boluses needed between two groups. Maternal complications such as nausea and vomiting were comparable between the groups. Neonatal outcome APGAR scores were above 7 in all newborn babies.

Conclusion: Single bolus of 6mcg norepinephrine was found as effective as phenylephrine in the management of hypotension following spinal anaesthesia during caesarean section. The neonatal outcomes were similar in both the groups.

Keywords: Spinal Anaesthesia, Caesarean Section, Norepinephrine, Phenylephrine, Hypotension.

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Introduction

Subarachnoid block (SAB) is most used regional anaesthesia technique in the world. It is a quick and effective technique with predictable and reliable benefits, and it has been the anaesthesia of choice for lower segment caesarean section (LSCS) until and unless it is contraindicated.

Hypotension is a common side effect of spinal anaesthesia for caesarean section, with an incidence of up to 71% [1]. Maternal hypotension produces unpleasant symptoms such as nausea, vomiting, and dizziness. Prompt treatment of hypotension with intravenous fluids and vasopressor is necessary to avoid detrimental maternal effects. Use of vasopressors, which lead to an increase in systemic vascular resistance and rise in mean arterial pressures, have been traditionally used for the prevention and management of hypotension after spinal anaesthesia.

The aim of the study to compare phenylephrine with norepinephrine boluses for the treatment of post spinal hypotension during elective caesarean section.

We hypothesized that Single bolus Norepinephrine is as effective as phenylephrine for treatment of hypotension following spinal anaesthesia during elective caesarean section.

Our research question was, in patients undergoing elective caesarean section under spinal anaesthesia whether Norepinephrine is superior to phenylephrine in preventing hypotension. Primary objective was to measure number of Phenylephrine and Norepinephrine boluses required to treat post spinal hypotension during Elective caesarean section. Secondary objective was to measure APGAR scores in the newborn.

Materials and Methods

A prospective, randomized, double blinded study will be conducted after obtaining ethical committee clearance, registration done for CTRI/2022/082044705. 60 patients who were belonging to American Society of Anaesthesiologist physical status (ASA PS II) in age group 20- 35 years undergoing elective caesarean section under spinal anaesthesia will be selected, based on inclusion criteria after obtaining written informed consent.

On the previous day of surgery, after thorough pre anaesthetic evaluation of patients, written informed consent was taken and patients were premedicated with oral Ranitidine 300mg, ondansetron 4mg. On the day surgery, after confirming nil per oral status, in the preoperative room, 18-gauge IV cannula was secured, preloaded with Inj. Ringer lactate (10ml/kg). In the operation room, American Society of Anaesthesiologist standard monitors were connected, and baseline vitals were recorded. Lumbar puncture was performed under strict aseptic measures in lateral decubitus position at L₃-L₄ space with 25G Quincke's spinal needle. After ensuring free flow of cerebrospinal fluid, 2 ml of hyperbaric bupivacaine 0.5% was injected. Patient positioning was given, and a wedge is placed under right buttock and adequate padding was given.

Heart rate, systolic Blood pressure (BP), diastolic BP, mean arterial pressure (MAP), and oxygen saturation was monitored at baseline, then after spinal anaesthesia every 3 mins till fifteen minutes thereafter every 5 mins till the end of surgery. Oxygen was delivered through Hudson oxygen mask (5L/min) to all patients throughout the procedure. Maintenance fluids was given based on body weight.

The parturient were randomised into group P and group N by computer-generated

random sequence of numbers and concealed by closed envelope technique. Norepinephrine and Phenylephrine will be diluted and loaded in an identical coded 10-mL syringe to give Norepinephrine 6 µg/mL and Phenylephrine 100 µg/mL. An anaesthetist who was posted in the theatre used one of either vasopressor-labelled syringe to treat hypotension when the systolic blood pressure falls below 20% of baseline and collect the data for analysis. The patient and the investigator were blinded to the vasopressors that were used. Blood pressure and HR was monitored every 3 min till 15 min, and thereafter every 5 min till the end of surgery. After delivery of baby, 10 U of oxytocin was given as a slow infusion. Incidences of nausea, vomiting and the total doses of vasopressor and intravenous fluid infused intra operatively was noted.

Primary objective is to compare the number of intravenous bolus doses of phenylephrine and norepinephrine for the treatment of post spinal hypotension during elective caesarean delivery and secondary objective is to compare APGAR score in the newborn.

Based on results of previous study, [9] sample size estimated by keeping power at 90%, and confidence level at 99%, a sample size of 52 (26 cases per group) were needed in each group. Considering potential dropouts or missing data, the sample size was increased to 5% approximately 27 in each group.

Norepinephrine being a very sensitive drug the power and confidence level kept high for sample size estimation.

Data was entered into Microsoft excel data sheet and was analysed using statistical package for social science (SPSS) 22 version software. Categorical data was represented in the form of Frequencies and proportions. Chi-square test was used as test of significance for qualitative data. Normality of the continuous data was tested by Kolmogorov–Smirnov test and the Shapiro–Wilk test. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical Analysis and Sample

Results

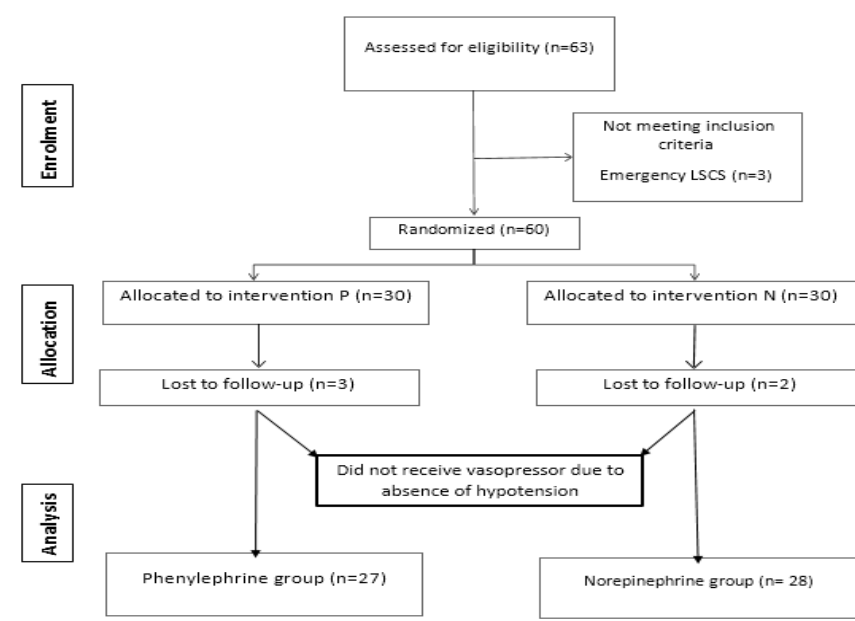


Figure 1: Consort Flow Chart

Table 1: Demographic data

	GROUP-P	GROUP -N	P value
Age	26.77 ± 3.936	25.47± 3.767	0.196
Weight	72.92±14.387	74.88±10.62	0.511
Height	148.34±5.286	145.20±4.91	0.823
Skin incision to Baby Delivery time (Sec)	342.33±63.17	270.53±54.42	<0.001*
Uterine incision to delivery time (Sec)	98.77±18.24	89.33±24.30	0.094
Total Duration of Surgery(min)	58.17±3.82	55.17±3.34	0.002*

Table 2: Total Number of Vasopressor Boluses

Total Number of Vasopressor Bolus used	Phenylephrine group P		Nor epinephrine group N	
	count	%	Count	%
One bolus	22	81.4%	25	89.25
Two boluses	5	18.5%	3	10.7%

27 mothers in phenylephrine group and 28 mothers in norepinephrine group developed hypotensive episodes. Single bolus of phenylephrine was given in 22/27 (81.4%) and two boluses were administered in 5/27 (18.5%).

In comparison, one bolus dose of norepinephrine was given in 25/28 (89.2%) and two doses in 3/28 (10.71%) to treat hypotensive episode.

Table 3: Mean number of vasopressor boluses

Phenylephrine group P		Nor epinephrine group N		P value
MEAN	SD	MEAN	SD	
1.185	0.388	1.107	0.309	0.3926

In phenylephrine group, mean number of vasopressor boluses needed were 1.185 ± 0.388 and in Norepinephrine group they were 1.107 ± 0.309 with p value 0.3926. The Number of boluses of vasopressor required to treat hypotension was lower in

Norepinephrine group when compared to phenylephrine group. There was no statistically significant difference in Number of Vasopressor Boluses needed between two groups.

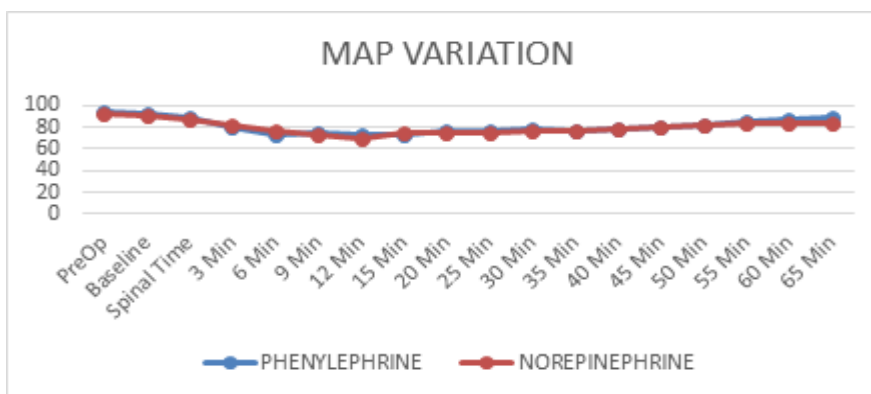


Figure 2: MAP Variation

Table 4: Mean Arterial Pressure Variation between Two Groups

Total Number of Vasopressor Bolus used	Group							
	Phenylephrine				Norepinephrine			
	Count	%	MEAN	SD	Count	%	MEAN	SD
one bolus	22	81.4%	1.185	0.388	25	89.2%	1.107	0.309
Two boluses	5	18.5%			3	10.7%		

Table 5: APGAR scores of neonates

APGAR	Group				P value
	Phenylephrine		Noradrenaline		
	Mean	SD	Mean	SD	
APGAR at 1 Min	7.97	0.18	8.00	0.00	0.321
APGAR AT 5 Min	9.00	0.00	8.97	0.18	0.321

APGAR scores were above 7 in all newborn babies.

Discussion

Cardiovascular changes during pregnancy along with aortocaval compression make 70 to 80% of pregnant patients susceptible to severe hypotension under SA during Caesarean delivery. The exact mechanism of spinal induced hypotension (SIH), and the knowledge about the loss of arteriolar tone and a significant fall of systemic vascular resistance (SVR) opened pathways to vasopressors for their therapeutic as well as prophylactic use for hypotension [2].

Recent guidelines of obstetric anaesthesia (2018) in their consensus statement emphasized the early and liberal use of vasopressors to prevent maternal hypotension aiming to maintain SBP at > 90% and avoid fall below 80% of the target baseline. A dependable vasopressor with a faster onset of action with a beneficial effect on maternal hemodynamic and fetal wellbeing without affecting the placental perfusion became a priority [3,4].

Vasopressors can either be administered as infusions or as intermittent bolus doses. Infusion regimens provide better hemodynamic control with minimal physical intervention [5]. But many clinicians favour bolus dosing because of the ease of the technique and limited or non-availability of infusion pumps in various centres [6].

In our study we compared bolus doses of norepinephrine and phenylephrine in the treatment of spinal-induced hypotension during caesarean section. The results of the study showed that single bolus of intravenous norepinephrine is effective in managing spinal hypotension with no detrimental effects on the neonatal and maternal outcome. The number of norepinephrine 6 mcg IV boluses needed to maintain blood pressure were significantly less than phenylephrine 100mcg IV bolus.

Various vasopressors have been used to treat spinal hypotension. Phenylephrine was the drug of choice in obstetric patients [7]. To treat spinal hypotension, the vasopressor may be given as intermittent boluses or as an infusion. Infusions allow tighter blood pressure control with less intervention required by the anaesthetist [8]. The use of intermittent boluses of the drug may be feasible in poor-resource settings where infusion pumps are not available or are only available in limited numbers, and hence cannot be available to all parturient who undergo a caesarean section. Hence, bolus doses of phenylephrine are used in many centres to treat spinal-induced hypotension though phenylephrine infusions are found to be better than boluses. Another advantage of the use of norepinephrine is that it is cheaper than phenylephrine. There was a concern regarding the use of

norepinephrine in the peripheral vein. But no signs of ischaemic complications in the limbs were reported by its use through a peripheral vein.

In our study mean number of phenylephrine boluses (100 mcg) 1.185 ± 0.388 and norepinephrine boluses (6mcg) were 1.107 ± 0.309 with a p value of 0.392, required treat hypotension post spinal anaesthesia. In a study done by Puthenveetil N. et al [9] mean number of phenylephrine boluses (50mcg) were 2.88 ± 1.061 and norepinephrine boluses (4mcg) were 1.40 ± 0.577 . In a study done by Anne Doherty et al [10] Phenylephrine infusion (120 $\mu\text{g}/\text{min}$) versus bolus (120 mcg) regimens during caesarean delivery under spinal anaesthesia. The infusion group received significantly more phenylephrine 613 μg versus bolus 454 μg with ($P < 0.001$). The infusion regimen required a higher total dose of phenylephrine to maintain maternal arterial blood pressure at baseline. In our study mean number of boluses were less because we used 100mcg phenylephrine IV bolus and norepinephrine 6mcg IV bolus.

In another study [11] comparing Norepinephrine 0.05 mcg/kg/min with phenylephrine 0.75 mcg/kg/min infusion for prophylaxis against post-spinal anaesthesia hypotension during elective caesarean delivery, norepinephrine effectively maintained maternal SBP during caesarean delivery under spinal anaesthesia with lower number of physician interventions, and likely less incidence of reactive hypertension and bradycardia compared to phenylephrine. In our study mean number of boluses were less because we used 100mcg phenylephrine IV bolus and norepinephrine 6mcg IV bolus, our results were concordance with this study, but we used Norepinephrine (6 $\mu\text{g}/\text{ml}$) versus Phenylephrine (100 $\mu\text{g}/\text{ml}$) in intermittent bolus doses.

Warwick D et al¹² conducted a study in 104 pregnant women undergoing elective

LSCS under SAB. One group received 0 to 5 $\mu\text{g}/\text{min}$ of norepinephrine and the other received 0 to 100 $\mu\text{g}/\text{min}$ of phenylephrine. The rate of vasopressor was greater in norepinephrine group (0.47ml/min) than in the phenylephrine group (0.39 to 0.58 ml/min). The incidence of nausea and vomiting was 6.1 % in norepinephrine and 3.8 % in phenylephrine group. The neonatal scores in both the groups were > 7 at 1 min and 5 min¹², in our study APGAR scores were above 7 in all newborn babies in both the groups, our study results were concordance with the study.

Kanika goel et al [13] conducted a study to compare norepinephrine and phenylephrine for maintenance of hemodynamics following SAB in LSCS patients, study includes 200 patients, phenylephrine 100 $\mu\text{g}/\text{mL}$ (Group A) or norepinephrine 5 $\mu\text{g}/\text{mL}$ with a infusion of the study solution was initiated at the rate of 30 mL/h. The infusion rate of PE was kept within the limits of 0 to 60 mL/h [0–100 $\mu\text{g}/\text{min}$] and that of NE within 0 to 60 mL/h [0–5 $\mu\text{g}/\text{min}$]. Parturients in group A received $370 \pm 112.6 \mu\text{g}$, whereas group B parturients received $18.4 \pm 7.4 \mu\text{g}$ of study drug, with a p value of 0.666. A statistically significant higher amount of drug (in μg) was received by the parturients in group A in comparison to the parturients in group B. The neonatal scores in both the groups were > 7 at 1 min and 5 min, in our study APGAR scores were above 7 in all newborn babies in both the groups, our study results were concordance with the study.

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

Conclusion

Single bolus of 6mcg norepinephrine was found as effective as phenylephrine in the

management of hypotension following spinal anaesthesia during caesarean section. The neonatal outcomes were similar in both the groups.

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