

# A Comparative Study to Evaluate the Effect of Norepinephrine and Phenylephrine in the Treatment of Post Spinal Hypotension for Caesarean Section

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## ABSTRACT

**Background:** Maternal hypotension due to spinal anaesthesia in caesarean section is commonly seen. Alongwith fluid loading, phenylephrine is used to manage the hypotension. However, this drug is associated with cardiovascular side effects.

**Methods:** This is a prospective double blinded study which was conducted on 100 term parturients scheduled from elective caesarean section under spinal anaesthesia, randomly assigned into two groups. After spinal anaesthesia patients of group N and P were treated with norepinephrine (5mcg) and phenylephrine (50mcg) respectively as an IV bolus for hypotension. Blood pressure, heart rate, number of bolus doses given, and neonatal APGAR score was noted.

**Results:** Patients of both groups were comparable with respect to haemodynamic parameters (HR, SBP, DBP, AND MAP). Incidence of bradycardia was higher in group P (22%, n=11) compared to group N (14%, n=7). Neonatal APGAR scores at different time intervals were similar in both groups.

**Conclusion:** Intermittent boluses of norepinephrine were effective in the treatment of spinal anaesthesia induced hypotension during caesarean section and can be considered as an alternative to phenylephrine.

Caesarean section is performed under spinal anaesthesia (SA) to prevent airway related complications of general anaesthesia (GA) and prevent neonatal drug transfer. It is however associated with maternal hypotension in upto 74% of cases. The hypotension is a result of reduced peripheral vascular resistance, decreased cardiac output and reduced venous return. This can in turn cause deleterious effects in both mother and foetus. Nausea, vomiting and even cardiovascular collapse can lead to maternal mortality. The placental bed is a low resistance system and the blood flow is directly proportional to maternal blood pressure (BP). Foetal effects such as hypoxia and acidosis may occur due to diminished uteroplacental perfusion. Phenylephrine (PE) is the drug of choice to treat spinal induced hypotension as it causes lesser foetal acidosis than ephedrine. It increases the blood pressure by increasing the systemic vascular

resistance, however we cannot consider this as an ideal drug as it causes reflex bradycardia and reduction in cardiac output since it is devoid of beta-adrenergic receptor activity. In a compromised maternal/foetal state, PE induced bradycardia and reduced cardiac output may further lead to deleterious effect in both mother and foetus. Norepinephrine (NE) with both alpha- and beta-adrenergic receptor activity for treatment of maternal hypotension is postulated to have lesser cardiovascular side effects. Though its use in septic shock is well established, there are very few studies to evaluate its effects on maternal hemodynamic and foetal wellbeing [1-2].

## Methods

This prospective double blinded hospital-based study was conducted from May 2017- May 2019 at a tertiary

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care hospital in Kolhapur, India. Upon obtaining ethical clearance from institutional ethical committee, the study was performed on 100 term parturient posted for elective caesarean section under spinal anaesthesia. Patients of age 18-35 years, height > 140 cm, weight < 100kg and belonging to ASA grade I and II were included following a written, informed consent in the study. Subjects who underwent emergency caesarean section, GA or inadequate spinal block, cases of pre-eclampsia, diabetes were excluded from the study.

Allocation of patients into the treatment group N (NE) and group P (PE) was randomized using a sealed envelope method. Before spinal anaesthesia allocation number was used to determine vasopressor, which would be given. The drugs were prepared in a concentration of 5mcg/ml of NE and 50mcg/ml of PE in a 10 ml syringe labelled as 'vasopressor' by a different anaesthesiologist who was not participating in the procedure.

All patients were advised to remain nil per oral for 6 hours and administered Inj. metoclopramide 10mg and Inj. ranitidine 50mg intravenous through 20G IV cannula in the morning, on the day of surgery. In operation theatre, ECG, pulse oximetry and non-invasive blood pressure (NIBP) were attached and baseline vitals were recorded. Patients were co-loaded with Ringer lactate solution at rate 4ml/kg/hr and then spinal anaesthesia was administered in sitting position. Hyperbaric bupivacaine 12mg was injected using 25 G spinal needle at L2-L3 or L3-L4 intervertebral space. Patient was then given supine position with wedge under the buttock and level of blockade was assessed with pin prick sensation, 5 minutes after the intrathecal injection. Supplemental oxygen was given through facemask. Blood pressure (BP) and heart rate (HR) were recorded every minute up to the time of delivery and every three minutes after that. A fall in Systolic BP (SBP) >20% from baseline considered as hypotension and treated with bolus dose of NE (5mcg) or Phenylephrine (50mcg). Dose was repeated after 3 minutes if hypotension persisted. Incidence of bradycardia (HR < 60beats /minute and hypertension were noted. A bolus of 0.6 mg of Inj. Atropine 0.6mg was given if heart rate dropped to <50/min. Umbilical venous sample was sent for blood gas analysis and neonatal APGAR scores were noted. An infusion of 500 ml 0.9% Normal Saline with 10 Units oxytocin was started after delivery of the baby.

### Sample Size Calculation

Sample size estimation was done with an 80% power at 95% level of significance, to detect a 30% incidence of hypotension, the sample size should be 40 patients per study group. To account for the drop-out rate, we included 50 patients in each of the group N and P.

### Statistical Analysis

Data was analysed using R studio V 1.2.5001 software. Continuous variables were expressed as mean +/- standard deviation whereas categorical variables were expressed in percentage and frequency. Wilcoxon-sign-rank-test and independent sample t test were used to find difference between mean. P < 0.05 was considered statistically significant.

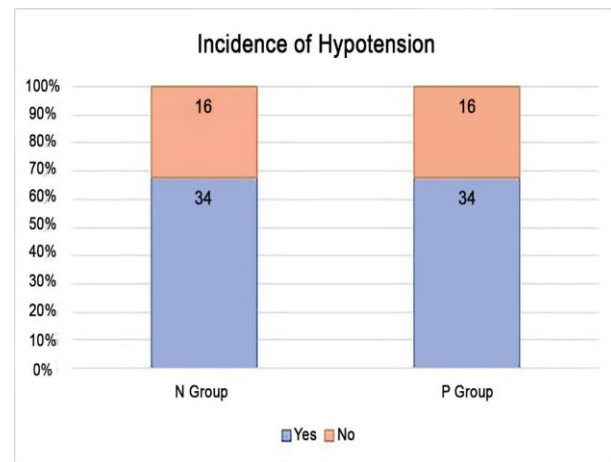
## Results

Demographic data in both the groups N and P are similar (Table 1).

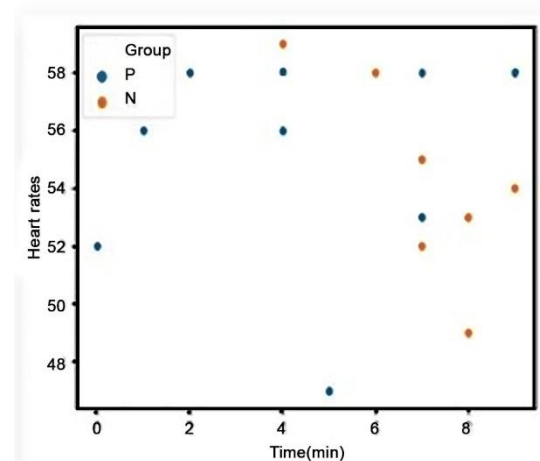
The incidence of hypotension in both groups is found to be similar (Figure 1).

Higher incidence of maternal bradycardia was noted in group P compared to group N maximum being at around 4minutes after administration of SA (Figure 2).

**Figure 1- Frequency distribution incidence of maternal hypotension in both N and P Group**



**Figure 2- Frequency distribution of incidence of maternal bradycardia in each group**



From (Table 2), we conclude that at 5% level of significance there is no statistically significant difference in proportion of Incidence of bradycardia in both N and P group.

From (Table 3), we conclude that at 5% level of significance, there is no statistically significant difference in vasopressor doses used in both P and N group.

From (Table 4), we can conclude that at 5 % level of significance there is statistically insignificant difference in mean of APGAR Scores in both N and P Group. No neonates in both the groups had APGAR score >9 at 5minutes.

**Table 1- Demographic Variables**

Variable	N Group	P Group	P value
Age	23.98±2.49	23.9±2.99	0.5771
Weight	58.38±7.35	59.56±8.02	0.4534
Height	152.56±5.28	152.48±5.40	0.432

**Table 2- Summary Table of proportion test in case of incidence of maternal bradycardia**

Incidence of bradycardia	N Group		P Group		P value
	Frequ ency	%	Frequ ency	%	
	7	14%	11	22%	0.4349

**Table 3- Summary table of Study of Vasopressor doses used in both groups**

Doses	N Group	P Group	P value
	2.62±2.87	2.4±2.29	0.986

**Table 4- Summary table of APGAR Score in each group**

APGAR Scores	N Group	P Group	P value
0 minute	6.67±0.51	6.78±0.42	0.3112
1 minute	7.65±0.52	7.78±0.42	0.2198
5 minutes	8.63±0.49	8.78±0.42	0.11

## Discussion

The study was conducted to compare the effect of NE and PE for treatment of hypotension after SA for elective caesarean delivery. Hypotension after SA needs intervention to maintain the normotensive state beneficial for both maternal and foetal well-being. This includes administration of IV fluids and vasopressors. Though PE, a pure alpha agonist is the drug of choice to treat hypotension in obstetric patients the search for ideal vasopressor continues [3]. PE is known to produce and hypertension and reflex bradycardia, often requiring the use of vagolytics in the mother.

Some researchers prefer NE to treat spinal hypotension [4-6], while some have studied the effect of NE in prevention of spinal hypotension [7]. NE is a potent alpha receptor agonist with beta activity. Not only does it

increase peripheral vascular resistance but also constricts capacitance vessels which have beta adrenergic receptors [5]. Though presumed to produce less maternal bradycardia, further research is required, hence we have attempted to study the effects of NE and compare it with PE in obstetrics patients.

Our study did not show any significant difference in demographic data of height, weight, and age of patients among both the groups. Similarly, no significant difference was seen in hemodynamic baseline parameters of HR, SBP, Diastolic BP and mean arterial pressure.

Both the vasopressors have short half-life, hence preferred to be administered as infusions. Intermittent bolus doses can be used in resource poor setting where infusion pumps are not available [5]. A word of caution is necessary when administering NE as a bolus through peripheral line which may extravasate and cause necrosis. We have noted no incidence of thrombophlebitis or extravasation in our study. Similar observations have been put forth by other researchers [1].

Ngan Kee and Ngan Kee et al., noted that 4mcg and 6 mcg of NE is equipotent to 50 mcg and 100mcg of phenylephrine respectively [8-9]. Mohta et al concluded that NE is 11 times more potent than phenylephrine [6]. In our study we compared 5mcg of NE with phenylephrine 50mcg. The number of bolus doses required for NE (2.62+/-2.87) and PE (2.4+/-2.229) to treat the incidents of hypotension was not different statistically (P=0.986) which were similar to results obtained by Puthenveetil et al. [1].

Though the incidence of bradycardia, recorded as HR <60/min was more P group (22%) than N group (14%) it was statistically not significant (P=0.43). Phenylephrine has been studied in doses from 20-100mcg. Studies find higher incidence of bradycardia with doses of 100mcg [10]. In our study we have used 50mcg which might be a reason for lower incidence of bradycardia seen in P group. Ngan Kee found lower incidence of bradycardia and increased cardiac output with the use of NE [8]. No tachycardia and hypertension were observed in both the groups.

Neonatal outcomes as noted by APGAR score was similar at all intervals and no baby had a score >9 at 5 minutes from delivery. The umbilical venous samples showed pH above 7.3 in both groups. Similar outcomes were noted by other researchers [1].

The limitation of this study is a limited sample size, hence effects of these drugs on maternal physiology needs to be studied further.

It can be concluded that the bolus of NE (5µg) showed similar efficacy compared with phenylephrine (50µg) in the maintenance of normal maternal hemodynamic parameters and neonatal outcome. Therefore, bolus NE can be considered as an alternative to PE bolus.

## Conclusion

It can be concluded that the bolus of NE (5µg) showed similar efficacy compared with phenylephrine (50µg) in the maintenance of normal maternal hemodynamic parameters and neonatal outcome. Therefore, bolus NE can be considered as an alternative to PE bolus.

## References

- [1] Puthenveetil N, Sivachalam SN, Rajan S, Paul J, Kumar L. Comparison of norepinephrine and phenylephrine boluses for the treatment of hypotension during spinal anaesthesia for caesarean section - A randomised controlled trial. *Indian J Anaesth.* 2019; 63(12):995-1000.
- [2] Ngan Kee WD, Lee SW, Ng FF, Tan PE, Khaw KS. Randomized double-blinded comparison of norepinephrine and phenylephrine for maintenance of blood pressure during spinal anaesthesia for caesarean delivery. *Anesthesiology.* 2015; 122(4):736-45.
- [3] Ngan Kee WD. The use of vasopressors during spinal anaesthesia for caesarean section. *Curr Opin Anaesthesiol* 2017; 30(3):319-25.
- [4] Wang T, He Q, Zhang W, Zhu J, Ni H, Yang R, et al. Determination of the ED50 and ED95 of intravenous bolus of NE for the treatment of hypotension during spinal anaesthesia for cesarean delivery. *Exp Ther Med.* 2020; 19(3):1763-1770.
- [5] Sharkey AM, Siddiqui N, Downey K, Ye XY, Guevara J, Carvalho JCA. Comparison of Intermittent Intravenous Boluses of Phenylephrine and Norepinephrine to Prevent and Treat Spinal-Induced Hypotension in Cesarean Deliveries: Randomized Controlled Trial. *Anesth Analg.* 2019; 129(5):1312-8.
- [6] Mohta M, Dubey M, Malhotra RK, Tyagi A. Comparison of the potency of phenylephrine and NE bolus doses used to treat post-spinal hypotension during elective caesarean section. *Int J Obstet Anesth.* 2019; 38:25-31.
- [7] Onwochei DN, Ngan Kee WD, Fung L, Downey K, Ye XY, Carvalho JCA. Norepinephrine Intermittent Intravenous Boluses to Prevent Hypotension During Spinal Anaesthesia for Cesarean Delivery: A Sequential Allocation Dose-Finding Study. *Anesth Analg.* 2017; 125(1):212-8.
- [8] Ngan Kee WD. A Random-allocation Graded Dose-Response Study of Norepinephrine and Phenylephrine for Treating Hypotension during Spinal Anaesthesia for Cesarean Delivery. *Anesthesiology.* 2017; 127(6):934-41.
- [9] Ngan Kee WD, Khaw KS, Tam YH, Ng FF, Lee SW. Performance of a closed-loop feedback computer-controlled infusion system for maintaining blood pressure during spinal anaesthesia for caesarean section: a randomized controlled comparison of norepinephrine versus phenylephrine. *J Clin Monit Comput.* 2017; 31(3):617-23.
- [10] Jaitawat SS, Partani S, Sharma V, et al. Prophylactic administration of two different bolus doses of phenylephrine for prevention of spinal-induced hypotension during cesarean section: A prospective double-blinded clinical study. *Journal of Obstetric Anaesthesia and Critical Care.* 2019; 9:81-7.