Original Article

Comparison of norepinephrine and phenylephrine infusions for maintenance of haemodynamics following subarachnoid block in lower segment caeserean section

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ABSTRACT

Background and Aims: Phenylephrine is the vasopressor of choice in spinal anaesthesia–induced maternal hypotension. However, it results in reflex bradycardia and decrease in cardiac output (CO), an effect that is perhaps less evident with the use of norepinephrine. We sought to evaluate the effect of phenylephrine and norepinephrine infusion on maternal systolic blood pressure (SBP), heart rate (HR), intraoperative nausea vomiting (IONV) and fatal Apgar scores. **Methods:** A randomised double-blind study was conducted on 200 American Society of Anesthesiologists (ASA) II–III parturients undergoing caesarean section under subarachnoid block (SAB) who were randomised to two groups A and B to receive variable rate, manually controlled infusions of phenylephrine and norepinephrine targeting maintenance of SBP to 100% of the baseline value. Maternal haemodynamics especially episodes of hypotension, IONV and vasopressor consumption were observed and recorded. **Results:** A statistically significant trend of lower SBP was observed during the first 6 min following intrathecal injection in group A (P value – 0.000). Though a greater number of parturients experienced ≥1 episode of hypotension in Group A vs Group B (13% vs 9%), the difference was, however, statistically insignificant. The incidence of bradycardia was higher in group A than in group B (16% vs 1%) and was found to be statistically significant ($P < 0.05$). The episodes of hypertension, IONV, maternal vasopressor consumption and neonatal Apgar score were comparable among both the groups. **Conclusion:** A dilute 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.

Key words: Caesarean section, norepinephrine, phenylephrine, spinal induced hypotension

INTRODUCTION

Subarachnoid block (SAB) is the technique of choice for elective caesarean section; however, it does result in hypotension in the vast majority of parturients if not actively prevented.[1] Thus, the routine use of vasopressors has been highly recommended for preventing post-spinal hypotension in parturients undergoing caesarean delivery. Phenylephrine (PE), a potent alpha-adrenergic receptor agonist, is the current gold standard vasopressor recommended for the prevention and treatment of maternal spinal-induced hypotension in parturients undergoing caesarean section under SAB. PE causes slowing of maternal heart rate (HR) and corresponding decrease in cardiac output (CO).[2] There have been growing concerns that the reflex slowing of heart rate, a

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surrogate marker of CO, may result in compromised uteroplacental perfusion, potentially adversely affecting a compromised foetus.[3]

Norepinephrine (NE), a potent alpha-adrenergic receptor agonist with relatively weak agonistic activity at beta-adrenergic receptors, is being considered as an alternative to PE as it causes lesser degree of bradycardia with minimal decrease in cardiac output due to its mild beta-agonist activity.[4]

Studies have evaluated the use of cumbersome computer feedback infusions of PE and NE as well as manual PE and NE infusion in their settings.[5] Data on the use of manual infusions of PE and NE is scarce for our subset of the maternal population. We proposed to compare the effect of manually controlled variable rate infusions of phenylephrine with norepinephrine on maternal haemodynamics, intraoperative nausea vomiting, and foetal outcome in our population group of parturients undergoing caesarean section under SAB. We hypothesised that an infusion of norepinephrine would be more effective for maintaining blood pressure with a greater heart rate in comparison to phenylephrine.

METHODS

A randomised double-blind observational study was conducted after approval by institutional Ethics Committee on a total of 200 American Society of Anesthesiologists (ASA) II and III full-term singleton parturients scheduled for lower segment caesarean section under SAB randomly allocated into either of two study groups of 100 parturients each by computer-generated randomisation codes contained in sealed, sequentially numbered envelopes. The study was registered at the Clinical Trials Registry-India [CTRI number- CTRI/2018/04/013430].

Patients with cardiac morbidities such as rheumatic heart disease, coronary artery disease, renal impairment, and hypertensive disorders of pregnancy were excluded from the study. Standardised anaesthetic care was provided according to institutional standards including fasting, antacid premedication, and non-invasive haemodynamic monitoring. After arrival in the operating room, parturients were positioned in the supine position with a 15-30° left lateral tilt. Routine monitoring including 5 lead electrocardiography (ECG), non-invasive blood pressure (NIBP) and pulse oximetry were started. Mean values of HR and NIBP were calculated and taken as baseline values. Baseline SBP was taken as an average of three consecutive measurements with a difference of <10%.

Under all aseptic precautions, SAB was performed with the patients in the right lateral position using a 26-G Quincke's spinal needle and 0.5% bupivacaine (1.7 mL) with 25 μg (0.5 mL) fentanyl injected intrathecally. At the start of intrathecal injection, the patient was rapidly coloaded with a balanced salt solution to a maximum of 2 litres after which the flow was reduced to maintenance rate.

The parturients were randomised into either of the two groups using computer-generated codes contained in sealed, sequentially numbered envelopes [Figure 1]. Infusion of the study solution was started as soon as SAB was administered. A solution of either phenylephrine 100 μg/mL (Group A) or norepinephrine 5 μg/mL (Group B) was prepared in 50 mL syringes and administered through a dedicated intravenous cannula.

The concentration of study solutions was chosen based on the potency ratio of 20:1 (NE:PE) as determined in previous clinical studies.[6,7]

The 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 μg/min] and that of NE within 0 to 60 mL/h [0–5 μg/min].[5,7] The automated NIBP cycling time was kept at 1 min interval after intrathecal injection until delivery. Study infusion was regulated targeting NIBP at 100% of baseline SBP. If NIBP was ≤80% of baseline, the infusion rate was doubled to 60 mL/h. Rescue boluses of 1 mL each were administered till the subsequent SBP readings remained ≤80% of baseline.[8] Hypotension was defined as SBP ≤80% of baseline or an absolute value less than 100 mm Hg, and the number of such episodes were recorded.[9] Episodes of hypertension defined as an SBP of ≥120% were treated by stopping the study solution and restarting at 30 mL/h when the SBP was less than 120%.[8] The total number of rescue boluses given and total volume of study solution given via the syringe pump up to the time of delivery was recorded. Bradycardia defined as HR <50 beats per min (bpm) was treated by stopping the study solution if associated with SBP more than or equal to baseline.[8] Bradycardia associated with SBP less than baseline was treated with intravenous atropine 0.6 mg.[8] The study was

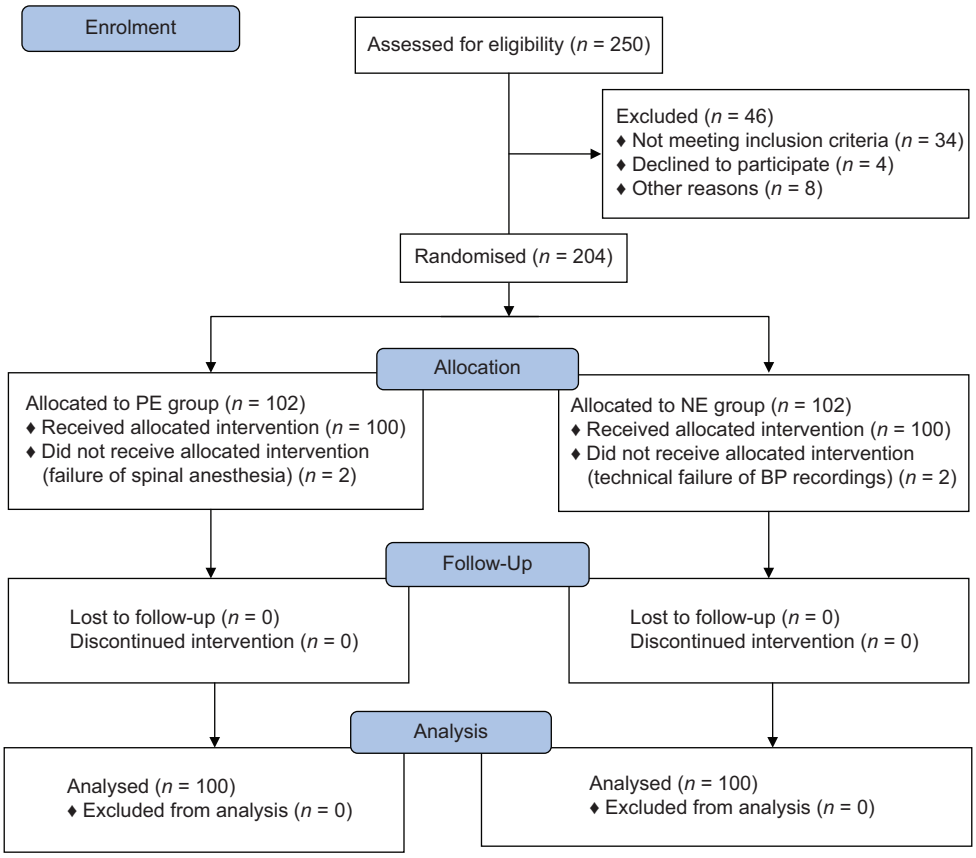

Figure 1: CONSORT Diagram

terminated on the delivery of the baby, and the study solution was then continued at the discretion of the attending anaesthesiologist. Episodes of intraoperative nausea and vomiting (IONV) were recorded using nausea vomiting score: 0: None; 1: Reported Nausea without vomiting; 2: Observed Vomiting.[8] IONV was treated with injection ondansetron 4 mg i/v at IONV score ≥1. Immediately after delivery, Apgar scores were assessed at 1 and 5 min, by an independent observer (Attending paediatrician blinded to the study group).

Discrete, categorical/classified data were presented in the form of either a number or a percentage [%]; whereas, the continuous data as its mean or standard deviation or its median and interquartile range, as per its normality or otherwise. The normality of quantitative data was checked by using Kolmogorov-Smirnov tests. Student *t*-test unpaired or Mann-Whitney U test was applied to compare two groups, depending upon the normality of the data. The categorical/classified data were compared using Chi-square or Fisher's Exact test, whichever was applicable. For comparison of haemodynamic (time-related variables), repeated measure analysis of variance (ANOVA) was applied. Student's *t*-test paired (for normally distributed data) or Wilcoxon Signed rank test (for skewed data) were used [for time-related variables]. All the statistical tests were two-sided and were performed at a significance level of 0.05. Analysis was conducted using International Business Machines Statistical Package for the Social Sciences (IBM SPSS) Statistics [version 22.0].

A power analysis was conducted using the software package, GPower (Faul and Erdfelder 1992). The alpha level used for this analysis was $P < 0.05$, and the beta was 0.20. By using an earlier study done by Ngan Kee *et al.* as a template and using the parameter episodes of hypotension, we expected similar results. The Power of the study was calculated to be 1 and with an effect size of 0.67 with a 10% chance of error for the total sample size 200.[10]

RESULTS

There was no difference between the groups in patient characteristics and surgical times [Table 1].

In group A, 13% of the parturients experienced one or more than one episode of hypotension as compared to 9% in group B. Figure 2 shows the

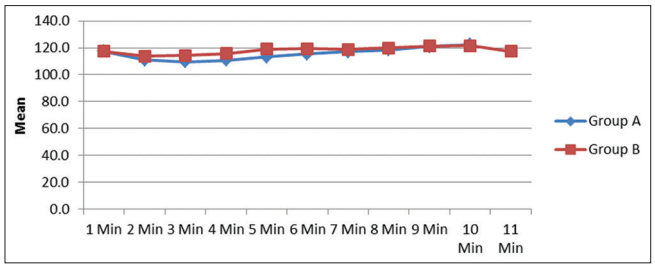

Figure 2: Trends in Intraoperative Systolic Blood Pressure (SBP) after intrathecal injection

Table 1: Patient characteristics and surgical times

	Phenylephrine group (*n*=100)	Norepinephrine group (*n*=100)	*P*
Age (yrs)	28.9 (3.8)	28.9 (4.0)	0.957
Weight (kg)	76.7 (7.9)	76.1 (9.1)	0.636
Height (cm)	163.3 (7.7)	163.6 (6.0)	0.757
Block height (T6)	52%	55%	0.671
Spinal-delivery time (min)	7 (6-8.0)	6 (6-8.0)	0.491

trends in the intraoperative SBP in both groups. The two groups were comparable in terms of hypotensive episodes (*P*- 0.363). The values of SBP were significantly lower in group A versus group B 2 minutes from the start of the study solution till 6 min ($P < 0.05$), however, they were comparable after 6 min of the start of the study solution, till the delivery of the baby. HR was greater over time in group B as compared to group A (*P*–-0.017) [Figure 3]. The incidence of bradycardia was lower in group B (1%) as compared to group A (16%). This difference was statistically significant with a *P* value of 0.001. Out of a total of 17 patients, one patient of the NE group and 7 patients of the PE group received injection atropine for bradycardia.

Hypertension (SBP >120% of baseline value) was seen in 4% of parturients in group A as compared to 3% in group B and was statistically comparable among the two groups. Both the groups were statistically comparable in terms of nausea (11% patients in group A and 7% patients in group B) (*P*-0.323). None of the parturients in either of the group complained of vomiting.

In group A, 10 parturients received ≥ one bolus as compared to 4 parturients in group B, but the difference was statistically insignificant ($P = 0.247$). The mean volume of the drug delivered to the parturients as rescue boluses, infusion and total amount were comparable in both the study groups. Parturients in group A received 370 ± 112.6 μg, whereas group B parturients received 18.4 ± 7.4 μg of study drug (rescue

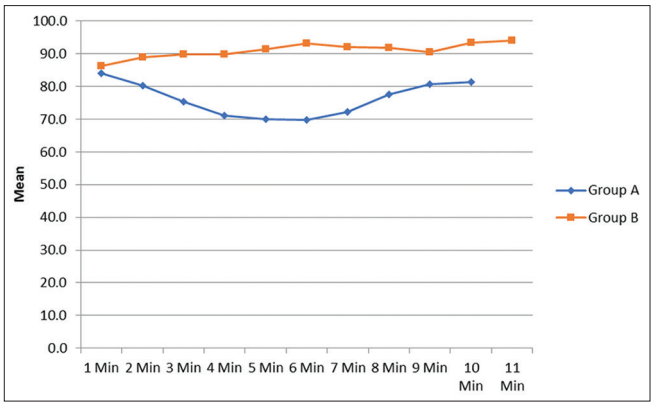

Figure 3: Trends in Intraoperative Heart Rate (HR) after intrathecal injection

boluses + infusion) [Table 2]. 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 reflecting an approximate ratio of 20:1 (phenylephrine: norepinephrine) [Table 3].

Neonatal outcomes assessed in the form of Apgar score at 1 and 5 min were comparable in both the groups ($P > 0.05$), and no patient had an Apgar score of less than 8 in either of the study groups.

DISCUSSION

We observed comparable efficacy of both PE and NE (no episode of hypotension in 87% of the patients in group A i.e.; PE vs 91% in group B i.e.; NE) in reducing the occurrence of spinal-induced maternal hypotension. Though a greater number of parturients experienced ≥ one episode of hypotension in group A vs group B (13% vs. 9%), these differences were statistically insignificant, further validating comparable efficacies of both vasopressors in maintaining stable blood pressures. A trend of relatively lower values of SBP was noted in our study in group A for the initial period from 2 min to 6 min which may be attributed to the initial lower dose of PE infusion (50 μg/min) used immediately after the institution of spinal anaesthesia. The mean volume of vasopressor drug delivered to parturients was comparable in both groups.

The overall reduced incidence of spinal hypotension was also reflected in the fewer and comparable episodes of nausea and vomiting limited to grade 1 observed among both the groups in our study. Our results thus corroborate that titrating vasopressors such as PE or NE to maintain maternal blood pressure near baseline values can reduce the incidence of maternal nausea and vomiting.[1,11] However, the lesser incidence of nausea

Table 2: Total amount of drug used (infusion + bolus) in ml								
Total amount of drug used (infusion + bolus) in ml	Group A		Group B		*Z*	*P*	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
	3.7	1.1	3.7	1.5	-0.440	0.660	0.644	0.663

SD-Standard deviation

Table 3: Total amount of drug used (infusion + bolus) in micrograms (µg)								
Total amount of drug used in µg	Group A		Group B		*Z*	*P*	95% Confidence Interval of the Difference	
	Mean	SD	Mean	SD			Lower	Upper
	370.0	112.6	18.4	7.4	-12.298	<0.001	0.000	0.030

SD-Standard deviation

and no episode of vomiting observed in our study compared to other studies may be due to the prevalent protocol in our obstetric units of administering injection metoclopramide and injection ranitidine to all parturients scheduled for caesarean delivery and to our study methodology of administering injection ondansetron at grade 1 of IONV.

The incidence of bradycardia in our study was higher in group A than in group B (16% vs 1% respectively; *P* value- 0.001). This statistically significant difference reflects two effects. The higher episodes of bradycardia observed in group A are a result of its α-adrenergic agonist properties which have a dose-related propensity to decrease heart rate (HR) and cardiac output (CO), occurring even when blood pressure is maintained at baseline.[11] On the contrary, NE has a lesser reduction in HR due to its both direct positive chronotropic and reflexive negative chronotropic actions.[12] Hence, the weak β-adrenergic agonist activity of norepinephrine counteracts the reflex slowing of HR. Similar findings have been reported by various investigators comparing NE with PE.[1,13] As HR is a surrogate marker of CO, the statistically significant reduced HR observed in group A can lead to decreased uteroplacental perfusion in compromised states such as severe pre-eclampsia or foetal distress.[1] Whereas higher SBP and HR trends in group B may theoretically benefit in the maintenance of uteroplacental perfusion.[1]

We derived our equipotent dosing protocol based on results of previous studies evaluating equipotency of PE:NE as 20:1 (100 µg:5 µg).[1,14-16] Many studies published lately have suggested lower potency ratio ranging from 16:1 to 13.1:1 Puthenveettil N *et al*. have used PE: NE in a further lower ratio of 50 µg:4 µg (12.5:1).[2] However, we adapted our infusion methodology from the algorithm protocol used by Ngan Kee *et al*. for computer-controlled infusions, in order to formulate an easy-to-titrate, manually controlled infusion protocol suited to the clinical settings of our study.[1,10,17]

We observed comparable and favourable neonatal outcomes reflected clinically by overall good Apgar scores with no score less than 8. However, our study has the limitation of not evaluating umbilical cord blood gases which could have further corroborated our favourable neonatal outcomes.

There are a few concerns and limitations of our study worth mentioning. There may be concern about the administration of NE via peripheral veins.[10,18] None of the patients in our study groups exhibited any extravasation or paleness on the site of dilute NE or PE infusion. It is imperative that a wide bore peripheral intravenous cannula be used, as in our study to deliver all dilute solutions of vasoactive drugs. There are concerns of investigator bias creeping in with the use of manually controlled infusions as they are labour intensive. This was eliminated to a large extent by blinding the study solutions, ensuring similar volumes for both study drug solutions and assigning an independent blinded observer to record and manage these infusions during the conduct of caesarean delivery.

Our major limitations are that we did not measure cardiac output and umbilical cord blood gases due to logistical issues in our clinical settings. Also, the blood pressure recordings were measured non-invasively which may be prone to artifacts and may not be precisely timed when there is an escalation of infusion rate or when rescue boluses were administered. We could have reduced this by performing error calculations. Inserting invasive lines is not currently an acceptable norm for uncomplicated caesarean deliveries. Perhaps, future studies in parturients with severe pre-eclampsia or conditions of reduced uteroplacental flow or severe maternal cardiovascular states may justify the use of invasive

arterial monitoring and assist applicability of these results to this specific obstetric population.

CONCLUSION

Hence, to summarise, the overall results of our study indicate a comparable advantage to the vasopressor efficacy of prophylactic manually controlled titrated infusion of NE analogous to PE using our simple infusion regimen. NE infusion provided an additional advantage of the reduction in the incidence of bradycardia and at the same time being equivalent to PE in preventing, maternal nausea and vomiting with favourable neonatal outcomes. We suggest more optimised and rigorous future studies before we can generalise and recommend the safe use of NE infusions in routine clinical practice.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. 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 anesthesia for cesarean delivery. Anesthesiology 2015;122:736-45.
2. Puthenveettil 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;63:995-1000.
3. Fakherpour A, Ghaem H, Fattahi Z, Zaree S. Maternal and anaesthesia-related risk factors and incidence of spinal anaesthesia-induced hypotension in elective caesarean section: A multinomial logistic regression. Indian J Anaesth 2018;62:36-46.
4. Shah PJ, Agrawal P, Beldar RK. Intravenous norepinephrine and mephentermine for maintenance of blood pressure during spinal anaesthesia for caesarean section: An interventional double-blinded randomised trial. Indian J Anaesth 2020;64:235-41.
5. Ngan Kee WD, Khaw KS, Ng FF, Tam YH. Randomized comparison of closed-loop feedback computer-controlled with manual-controlled infusion of phenylephrine for maintaining arterial pressure during spinal anaesthesia for caesarean delivery. Br J Anaesth 2013;110:59-65.
6. Carvalho B, Dyer RA. Norepinephrine for spinal hypotension during cesarean delivery: Another paradigm shift? Anesthesiology 2015;122:728-30.
7. Ngan Kee WD, Tam YH, Khaw KS, Ng FF, Critchley LA, Karmakar MK. Closed-loop feedback computer-controlled infusion of phenylephrine for maintaining blood pressure during spinal anaesthesia for caesarean section: A preliminary descriptive study. Anaesthesia 2007;62:1251-6.
8. Cooper DW. Caesarean delivery vasopressor management. Curr Opin Anaesthesiol 2012;25:300-8.
9. Klöhr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: Literature search and application to parturients. Acta Anaesthesiol Scand 2010;54:909-21.
10. Ngan Kee WD, Lee SWY, Ng FF, Khaw KS. Prophylactic norepinephrine infusion for preventing hypotension during spinal anesthesia for cesarean delivery. Anesth Analg 2018;126:1989-94.
11. Ngan Kee WD, Khaw KS, Ng FF. Comparison of phenylephrine infusion regimens for maintaining maternal blood pressure during spinal anaesthesia for Caesarean section. Br J Anaesth 2004;92:469-74.
12. Ferguson-Myrthil N. Vasopressor use in adult patients. Cardiol Rev 2012;20:153-8.
13. Dong L, Dong Q, Song X, Liu Y, Wang Y. Comparison of prophylactic bolus norepinephrine and phenylephrine on hypotension during spinal anesthesia for cesarean section. Int J Clin Exp Med 2017;10:12315-21.
14. Sjöberg T, Norgren L, Andersson KE, Steen S. Comparative effects of the alpha-adrenoceptor agonists noradrenaline, phenylephrine and clonidine in the human saphenous vein *in vivo* and *in vitro*. Acta Physiol Scand 1989;136:463-71.
15. Lindner KH, Seefelder C, Schirmer U, Beyer M, Georgieff M. Effect of phenylephrine bolus administration on global left ventricular function in patients with coronary artery disease and patients with valvular aortic stenosis. Anesthesiology 1993;78:834-41.
16. Goertz AW, Schmidt M, Seefelder C, Lindner KH, Georgieff M. The effect of phenylephrine bolus administration on left ventricular function during isoflurane-induced hypotension. Anesth Analg 1993;77:227-31.
17. Ngan Kee WD. A random-allocation graded dose-response study of norepinephrine and phenylephrine for treating hypotension during spinal anesthesia for cesarean delivery. Anesthesiology 2017;127:934-41.
18. Smiley RM. More perfect? Int J Obstet Anesth 2017;29:1-4.