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Comparison of Effect of Norepinephrine Versus Phenylephrine Prophylactic Boluses on Spinal Anesthesia-Induced Hypotension During Elective Cesarean Delivery: A Double-Blind, Randomized, Clinical Study

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Abstract

Background: Spinal anesthesia (SA) onset induces maternal hypotension, which can be managed by vasopressors like phenylephrine (PE). However, PE (α-adrenergic agonist) tends to reflexively decrease the heart rate (HR) and cardiac output (CO). Norepinephrine (NE), being an α-agonist with weak β-adrenergic activity, maintains the blood pressure (BP) with less tendency to decrease the HR and CO, and hence, may be a more useful alternative to PE.

Objectives: To compare the effects of prophylactic boluses of NE and PE on SA-induced hypotension during elective cesarean section, as well as assess the neonatal outcomes and adverse reactions.

Methods: Sixty parturient belonging to ASA class I and II, scheduled for elective cesarean section, were randomly allocated between 2 groups: (i) Group NE (n=30) which received 5 µg intravenous (IV) NE, and (ii) Group PE (n=30) which received 50 µg IV PE as prophylactic boluses immediately after patient repositioning. Rescue bolus interventions using 5 µg NE or 25 µg PE were given for hypotension, respectively. Maternal hemodynamic variables were measured non-invasively. Neonatal outcomes and adverse effects, if any, were also noted and compared.

Results: Pre-operative and post-operative hemodynamic parameters (HR, SBP, DBP, MAP, SpO2), adverse incidences (of hypotension, bradycardia, and nausea) as well as neonatal outcomes were comparable between the two groups (P>0.05). However, the number of patients who required additional rescue vasopressor boluses was significantly greater in Group PE than in Group NE (OR for 2 vs 0 bolus = 9.75; OR for 2 vs. 1 bolus = 11.1428).

Conclusion: NE was more efficacious in preventing SA-induced hypotension with better preservation of maternal HR than PE, and hence, can be considered as an alternative to PE.

Keywords: Spinal anesthesia; Phenylephrine; Norepinephrine; Parturition; Blood pressure; Obstetric surgical procedures.

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Introduction

Spinal anesthesia (SA) is preferred for most of the abdomino-pelvic surgeries, including cesarean sections, since it is a simple and safe technique with rapid onset, allows the patient to remain awake, avoids airway management problems besides providing postoperative analgesia.[1-4] Hyperbaric bupivacaine (0.5%) is extensively used for SA.[4,5] However, a common side effect of SA onset is maternal hypotension due to SA-induced venodilation leading to a reduction in venous return and hence, cardiac output (CO), eventually reducing uteroplacental perfusion, causing both maternal morbidities (nausea, vomiting, inadequate cerebral perfusion, decreased consciousness, respiratory depression, and cardiac arrest) as well as adverse fetal effects (impaired fetal oxygenation, asphyxial stress, and fetal acidosis as it depends on the maternal uterine artery pressure for adequate uterine blood flow).[6]

Due to the poor efficacy of non-pharmacological techniques (like left uterine displacement to decrease aortocaval compression, leg elevation, and prehydration/preloading) to efficiently manage hypotension, a vasopressor such as phenylephrine (PE) is usually required to maintain the blood pressure (BP) during SA.[7-8] However, PE is a potent α-agonist without β-adrenergic activity, causing a dose-related reflex decrease in the heart rate (HR) and CO, which may be harmful in the presence of a compromised fetus.[9]

Norepinephrine (NE) may be a useful alternative to PE since it is a potent α-agonist with weak β-agonist action, thus counteracting the baroreceptor response to the α-effects. It can, therefore, maintain the BP with a low tendency to decrease the HR and CO compared to PE. Although hypotension management during SA is listed by the manufacturer as an indication for the use of NE, there is limited information available for its use in obstetric patients.[9]

The objective of the present study was to compare the effects of prophylactic boluses of NE and PE on SA-induced hypotension during elective cesarean section, as well as to assess the neonatal outcomes and adverse reactions.

Materials and Methods

This double-blind, prospective, interventional, randomized, controlled, clinical study was conducted at the Department of Anesthesiology, Maharashtra, from December 2017 to May 2019, after obtaining ethical clearance from the Institutional Review Board.

Sixty female patients, aged 18-35 years, singleton parturient with gestational age >36 weeks, ASA I or II physical status, and planned for cesarean section under spinal anesthesia, were recruited into the study after obtaining a written informed consent. Pregnant females with multiple gestations, abnormal placentation, essential or pregnancy-induced hypertension, history of significant systemic disorders (cardiovascular, respiratory, renal, or central nervous system), coagulopathies, spinal sensory loss above T6 dermatomal level, allergy to drugs intended to be used in the study and any other contraindications for spinal anesthesia were excluded from the study. The included patients were randomly divided (using computer generated codes and sealed envelope technique) into 2 groups depending on which prophylactic intravenous (IV) vasopressor was to be given – phenylephrine (Group PE) or norepinephrine (Group NE). For the purpose of this study, hypotension was defined as >20% decrease in the baseline mean arterial pressure (MAP).

Pre-anesthetic examination - On the evening before surgery, all patients underwent clinical examination (history, general condition, airway assessment by Mallampati grading,[10] nutritional status, height, weight, cardiovascular, respiratory, central nervous system, and spine examinations) as well as lab investigations (complete blood count, random blood sugar. blood urea, serum creatinine, blood grouping, Rh typing, coagulation profile, and urine analysis for albumin, sugar, and microscopy).

Pre-surgical preparation - A peripheral IV line was secured in a forearm vein with an 18-gauge cannula and connected to a three-way stopcock. Patients were preloaded with 500 mL of Ringer's lactate prior to the scheduled surgery and premedicated with IV Ranitidine (50 mg) and IV Ondansetron (4 mg). Baseline parameters were recorded after 15 min. In the operation theater, a multiparameter monitor was connected to non-invasively record and monitor the HR, systolic BP (SBP), diastolic BP (DBP), MAP, electrocardiogram (ECG), and oxygen saturation (SpO2%). Oxygen supplementation was given via a clear face mask at a rate of 4 L/min.

Study drug preparation - 0.5 mL of commercially available preparation of PE (10 mg/mL) was added to 100 mL of 5% dextrose to obtain a solution containing 50 μg/mL PE; 2 mL of this PE solution (50 μg/mL) was taken in a 5 mL syringe and further

diluted with 2 mL of 5% dextrose yielding a 25 µg/mL solution of PE. A similar solution containing 5 µg/mL NE was prepared by adding 0.5 mL of commercially available preparation of NE (1 mg/mL) to 100 mL of 5% dextrose.

Spinal anesthesia - Under strict aseptic precautions and with the patient in left lateral decubitus position, a lumbar puncture was performed at the L3-L4 intervertebral space with a 25-gauge Quincke spinal needle, using a midline approach. After obtaining a free flow of clear cerebrospinal fluid, 2.2 mL of hyperbaric bupivacaine (0.5%) injection was administered. Immediately after the spinal injection, the needle was withdrawn, the patient turned supine with continuous maintenance of left uterine displacement using a wedge, and a prophylactic bolus of the test drug administered.

Test drug administration - Group PE received 50 µg of IV PE and Group NE received 5 µg of IV NE as a prophylactic bolus and an additional rescue bolus of 25 µg PE and 5µg NE, respectively, every time the fall in MAP was >20% from baseline.

Post-anesthetic assessment - Motor block was assessed using modified Bromage scale.11 Bilateral sensory loss up to the T6 dermatomal level was tested using pinprick. Failure to achieve a dermatomal block up to T6 or attaining a higher level of sensory loss led to exclusion of the case from the study. HR, SBP, DBP, and MAP were noted at 1-min intervals for the first 5 min after intrathecal administration of hyperbaric bupivacaine injection, then every alternate minute for 15 min and after that, every 5 min, till the end of surgery. Fall in BP >20% of the baseline MAP was treated with an additional rescue bolus of the same study drug. Fall in the HR to <60 beats per min (bpm) for >30 s was treated with incremental doses of 0.3 mg of IV atropine. Any incidence of nausea (reported by patients) or vomiting (observed by investigators) was recorded, and if not associated with hypotension, was treated with 10 mg of IV metoclopramide.

Neonatal outcome assessment - After delivery, 20 IU of oxytocin injection was added to 500 mL of normal saline and given slowly intravenously. Blood was collected from the umbilical artery and immediately sent for arterial blood gas (ABG) analysis to estimate the umbilical artery blood pH, pO2, pCO2, lactate, and base excess. The neonatal status was assessed by APGAR score12 at 1 and 5 min.

Post-operative assessment - Post-operative monitoring of HR, SBP, DBP, and MAP of the patient was continued in the post-anesthesia care unit every 15 min for 1 h.

Statistical analysis - A sample size of 30 in each group was calculated by assuming a power of 90%, alpha error of 0.05 with a standard deviation (SD) of 0.07. The data was collected, compiled, and analyzed using the statistical software R version 3.6.1. Categorical variables are represented as frequency table and continuous variables are represented as mean ± standard deviation form. Chi-square test was used to check the dependency between two categorical variables. For mean comparison, t-test/repeated measures analysis (mixed models) was used. P value of ≤0.05 indicated statistical significance.

Results

Comparison of the demographic parameters between the two groups is presented in Table 1. The age of the study participants ranged from 20-22 years, weight between 46-74 kg, and height between 150-170 cm. Using two-sample t-test, no significant differences in these parameters were found between the groups.

Table 2 shows the comparison of pre-operative and post-operative hemodynamic parameters between the two groups over various time points, derived using mixed-model analysis. Variance between the subjects was taken as a random effect, and group and time points as a fixed effect. There were significant differences in the means of pre-operative SBP (P<0.0001), DBP (P<0.0001), and MAP (P<0.0001) over different time points, but this difference was not significant between the groups. There was also a trend for the HR to be significantly greater in Group NE than Group PE at different time points (P value was 0.005795 for interaction effect). However, there was no significant difference in the mean values of post-operative HR, SBP, DBP, and MAP between the groups over time.

Comparison of incidences of adverse events between the two groups is presented in Table 3. None of the patients reported vomiting. The Chi-square test showed no significant difference between the two groups with respect to the incidences of hypotension (P=0.176), nausea, and bradycardia. It revealed a significant difference between the groups in the distribution of the number of rescue vasopressor boluses required. Significant odds ratios were reported. The odds of having 2 rescue vasopressor boluses than no (nil) vasopressor boluses were 9.75 (CI: 1.7167-55.3725) times for PE group compared to NE group. Also,

the odds of having 2 vasopressor boluses than 1 vasopressor bolus were 11.1428 (CI: 1.9238-64.5378) times for PE group compared to NE group.

Comparison of neonatal outcomes between the two groups is summarized in Table 4. No significant difference between the two groups was found using two-sample t-test with respect to birth weight, APGAR score at 1st and 5th minute, pH, pO2 and pCO2, lactate, and base excess (P>0.05). A significant difference was noted in the distribution of APGAR score at 1 min and 5 min but not in its distribution between the groups, upon applying the generalized estimating equations technique by taking Poisson family with AR1 correlation structure.

Table 1: Comparison of demographic parameters between the two groups.

Parameter	Group NE	Group PE	P P value
Age (years)	25.9±3.65	26.43±3.65	0.574
Weight (kg)	60.87±6.91	61.6±6.46	0.6727
Height (cm)	159.93±3.89	159.23±4.53	0.5232

NE: norepinephrine; PE: phenylephrine.

Table 2: Comparison of hemodynamic parameters between the two groups.

Parameters	Time points	Group NE	Group PE	P P value
Pre-operative heart rate	Baseline	87.17±5.59	89.29±7.01	0.263288[a] <0.0001[b] 0.005795[c]
	15 min	91.63±11.42	86.16±10.32	
	30 min	86.36±8.75	84.83±7.36	
	45 min	84.53±7.54	82.83±7.61	
	1 h	85.4±8.83	82.4±7.01	
Pre-operative systolic blood pressure	Baseline	121.80±9.75	120.86±9.47	0.2591[a] <0.0001[b] 0.6112[c]
	15 min	109.93±9.45	107.57±9.98	
	30 min	110.4±11.07	108.7±10.24	
	45 min	115.33±10.79	111.66±9.01	
	1 h	116.43±9.41	112.83±8.64	
Pre-operative diastolic blood pressure	Baseline	77.93±8.29	76.83±8.07	0.3221a <0.0001b 0.2307c
	15 min	68.56±8.21	64.83±8.47	
	30 min	68.8±9.23	65.7±10.48	
	45 min	70.43±8.67	69.66±7.81	
	1 h	71.9±6.21	72.2±5.58	
Pre-operative mean arterial pressure	Baseline	92.53±8.01	91.48±7.83	0.2719a <0.0001b 0.6397c
	15 min	82.35±8.07	79.08±8.29	
	30 min	82.67±9.29	80.03±9.65	
	45 min	85.4±8.94	86.75±7.45	
	1 h	86.75±6.75	85.74±5.93	
Post-operative heart rate	15 min	82.5±6.82	80.83±6.53	0.51193a 0.09869b 0.11673c
	1 h	81.2±6.37	80.8±5.38	
Post-operative systolic blood pressure	15 min	116.83±8.28	114.46±8.78	0.2569a 0.5158b 0.8966c
	1 h	117.03±7.47	114.76±7.61	
Post-operative diastolic blood pressure	15 min	72.26±5.72	73.13±5.52	0.5476a 1.000b 0.8595c
	1 h	72.33±5.56	73.07±4.53	
Post-operative mean arterial pressure	15 min	87.12±6.20	86.91±6.15	0.8689a 0.7999b 0.9184c
	15 min	82.5±6.82	80.83±6.53	

NE: norepinephrine; PE: phenylephrine a: P P value for comparison of groups; b: P P value for comparison over time; c: P P value for interaction effect of group and time.

Table 3: Comparison of incidences of adverse events between the two groups.

Parameter		Group NE (n=30) n (%)	Group PE (n=30) n (%)	P P value
Hypotension	Absent	13 (43.33)	8 (26.67)	0.176
	Present	17 (56.67)	22 (73.33)	
No. of rescue vasopressor boluses	Nil	13 (43.33)	8 (26.67)	0.01499MC
	1 bolus	13 (43.33)	7 (23.3)	
	2 bolus	2 (6.67)	12 (40)	
	3 bolus	2 (6.67)	3 (10)	
Bradycardia	Absent	29 (96.67)	25 (83.33)	0.01844MC
	Present	1 (3.33)	5 (16.67)	
Nausea	Absent	26 (86.67)	25 (83.33)	1MC
	Present	4 (13.33)	5 (16.67)	

NE: norepinephrine; PE: phenylephrine MC: P P value obtained by Monte-Carlo simulation.

Table 4: Comparison of neonatal outcomes between the two groups.

Parameter	Group NE	Group PE	P P value
pH	7.41±0.02	7.41±0.03	0.8419
pO2	94.91±2.71	93.74±3.14	0.1286
pCO2	39.93±1.74	39.63±1.99	0.5368
Lactate	1.5±0.26	1.56±0.25	0.3185
Base excess	-0.03 ± 1.217	-0.27 ± 1.311	0.478
Birth weight (kg)	2.68±0.23	2.69±0.34	0.895
APGAR at 1 min	7 (7,8)	7 (7,8)	<0.0001a
APGAR at 5 min	8.5 (8,9)	9 (8,9)	

NE: norepinephrine; PE: phenylephrine; pO2: Partial Pressure of Oxygen, pCO2: partial pressure of carbon dioxide; APGAR: Appearance, Pulse, Grimace, Activity, and Respiration a: P value for comparison between times.

Discussion

This prospective clinical study was conducted to compare the effects of prophylactic boluses of NE and PE on SA-induced hypotension during elective cesarean section, as well as to assess the neonatal outcomes and adverse reactions, if any. The usual approach to use vasopressors is reactive rather than proactive; however, since the SA-induced hypotension is hazardous to the mother and more so to the fetus, it is better prevented than treated. Hence, prophylactic vasopressors were used.

The demographic data were comparable in both the groups, thus avoiding confounding of the results. The hemodynamic parameters, adverse events incidences, and neonatal outcomes showed no significant differences between the groups, except odds of requiring rescue vasopressor boluses (PE>NE).

Various other researchers, who compared the roles of PE and NE in the management of SA-induced hypotension during cesarean surgeries, found similar results. Vallejo et al too noted that the maternal HR (P=0.17), SBP (P=0.25), DBP (P=0.15), CO (P=0.5), and stroke volume (P=0.5) were similar between the groups.[13] Dong et al observed no significant difference in the SBP over time (unlike the present study), but the HR at 2nd and 4th minute after SA was significantly higher in the NE group than PE group (P<0.05) indicating that NE is not only as effective as PE in preventing spinal hypotension but also has greater CO compared to PE.[6] Ngan Kee et al and Sharkey et al also reported that NE preserved maternal HR more effectively than PE (P=0.039) and had similar efficacy to PE in maintaining BP.[9,14]

Akin to the present study, no significant difference in the incidence of bradycardia was noted between the NE and PE groups by Vallejo et al (P=0.58).[13] However, it was found to be lower in the NE group by Dong et al (P<0.05), Ngan Kee et al (P<0.001), and Sharkey et al (P<0.001), which is quite contrary to the present study. Bradycardia seen with PE was not associated with hypotension but with a transient baroreceptor-mediated reflex mechanism. NE, on the other hand, may have annulled the bradycardia due to its weak positive chronotropic action by the stimulation of β-receptors.[6,9,14]

The present study also revealed that the incidence of hypotension was comparable between the two groups, but the number of patients who had more episodes of hypotension and thus required ≥2 rescue vasopressor boluses of the study drugs was significantly higher in the PE group than NE group. In line with these findings, Vallejo et al as well as Sharkey et al found no significant difference in the hypotensive incidences between patients on PE (65.8% and 39%, respectively) and those on NE (48.8% and 38%, respectively).[13,14] Sahu et al found an 85% prevalence rate for hypotension in similar settings, while McArthur et al found that 40-60% of women undergoing cesarean delivery needed treatment with vasopressor medications.[15,16] Sharkey et al also reported that the number of patients requiring additional vasopressor rescue boluses was significantly lower in NE group (7.2%) compared to PE group (21.4%) (P<0.03). This can be because, at term, the uterine vascular bed is maximally vasodilated and unable to autoregulate when the perfusion pressure is reduced. Consequently, a higher adrenoreceptor density renders uteroplacental blood flow potentially vulnerable to vasoconstriction induced

by α-adrenergic agonists like PE.[14] Contrary to the current study, the need for rescue boluses was comparable between both the groups (P=0.25) in Vallejo et al's study.[13]

The incidence of nausea, too did not show any significant difference between the two groups, in concordance with the results obtained by Dong et al (P=0.68), Ngan Kee et al (P=0.67), Vallejo et al (P=0.28), and Sharkey et al (P=0.57).[6,9,13,14]

The APGAR scores and measured umbilical artery metabolic markers were used to indicate the adequacy of placental perfusion, which showed no significant differences between the two groups, despite periods of maternal hypotension and transient HR reduction. This could be due to immediate correction of hypotension episodes and thus, the maintenance of uteroplacental perfusion in both the groups. APGAR scores at 1 and 5 min were >7 and pH never <7.2 in all patients. Similar findings have been reported by Dong et al, Ngan Kee et al, Vallejo et al, and Sharkey et al.[6,9,13,14] This has been explained by Robson et al who found that umbilical artery blood pH correlated well with maternal CO but not with BP itself.[17] Joupilla et al observed that IV preloading maintains the placental blood flow despite a moderate reduction in the maternal pressure, thus minimizing fetal acidosis.[18] In the present study, all patients were preloaded with 500 mL of Ringer's lactate solution, which probably would have maintained the placental flow during hypotensive episodes.

This study establishes that NE is more efficacious than PE in preventing SA-induced hypotension and maintaining the maternal HR, and hence, can be considered as an alternative to PE.

This study has its limitations in being a single-center study with a limited sample size. Multicentric, prospective studies with a larger sample size are encouraged to validate the results.

Conclusion

The hemodynamic profile offered by NE in preventing SA-induced hypotension during elective cesarean delivery is superior to PE with better preservation of maternal HR and decreased requirement of rescue vasopressor boluses. Neither of the drugs posed any adverse neonatal outcomes or unmanageable maternal side effects. Hence, NE can be considered as an effective alternative to PE.

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