Original Article

A Study of Phenylephrine Administration for the Prevention and Treatment of Hypotension in Cesarean Section during Spinal Anaesthesia: A Randomised Clinical trial

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Abstract

Background: Hypotension remains the most common complication following spinal anesthesia in cesarean sections. Despite using various preventive measures, hypotension occurs in most cases; vasopressors are often required. The current study evaluated the safety and efficacy of prophylactic phenylephrine infusion in preventing spinal anesthesia-induced hypotension in the Cesarean Section.

Materials and Methods: A total of 50 parturients aged 20-35 years with American Society of Anesthesiologists (ASA) grade II, scheduled for elective cesarean sections were randomly allocated into one of the two groups. Group A (n=25) received intravenous prophylactic phenylephrine infusion at 100µg/min for 3min after spinal anesthesia using a syringe pump. Each minute, systolic arterial pressure (SAP) was measured, and infusion stopped if SAP > baseline and continued if less than or equal to baseline systolic arterial pressure. Intravenous phenylephrine bolus 100µg was given when SAP decreased to <80% of baseline. Group B (n=25) received only intravenous phenylephrine bolus 100µg when SAP decreased to <80% of baseline. After 1 minute of spinal anesthesia, Heart Rate (HR), SAP, and diastolic blood pressure (DBP) were recorded every minute until the baby's extraction. After the delivery of the baby, APGAR scores at 1 minute and 5 minutes were noted. Umbilical artery blood was sent for analysis of the pH. The total volumes of study solutions given up to the time of delivery of the baby were recorded.

Results: Phenylephrine infusion decreased the incidence and frequency of hypotension compared with control and the phenylephrine dose was much higher in the infusion group than in the control group (p=0.0001). None of the patients had any incidence of nausea or vomiting. There was no significant difference in umbilical artery blood pH and no reduction in the APGAR scores. HR was significantly slower in the infusion group compared with the control group.

Conclusion: A prophylactic infusion of phenylephrine100 µg/min in patients receiving spinal anesthesia for elective cesarean delivery decreased the incidence of hypotension and without any deleterious neonatal outcome.

Keywords: Phenylephrine, Hypotension, Bradycardia, Spinal Anaesthesia, Cesarean section, APGR, Umbilical artery blood pH

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Introduction

Spinal anesthesia is the preferred anesthetic technique for cesarean sections nowadays to prevent general anesthesia-related complications like failed intubation, aspiration, and depressant effect of general anesthetics on neonates (1). However, the incidence of hypotension is 75-85% with this technique which is detrimental to both mother and fetus (2). A mother with hypotension is associated with nausea and vomiting and risks reduced consciousness, respiratory depression, pulmonary aspiration, and cardiac arrest (3). Hypotension had detrimental effects on neonates, such as decreased uteroplacental flow, impaired fetal oxygenation with asphyxia, and fetal acidosis (4). Preventive measures for hypotension include adequate preload (10-15ml/kg), lateral tilt, wedge, and vasopressors use (5). Ephedrine is the preferred vasopressor in cesarean sections. It has direct and indirect action mechanisms, stimulating mainly beta receptors (β1 and β2), causing increased cardiac output, heart rate, and systolic and diastolic blood pressure. However, it can cause supraventricular tachycardia, tachyphylaxis, and fetal acidosis (6, 7). Various studies have shown Ephedrine to be associated with a dose-related propensity to depress fetal pH and base excess. Phenylephrine is a selective α1 adrenergic agonist that is as effective as Ephedrine in treating spinal hypotension with a better neonatal outcome and fetal acid-base status (7-9). If tachycardia is undesirable, Phenylephrine may be better than Ephedrine. The APGAR scores and umbilical artery blood pH measurements were used to indicate the adequacy of placental perfusion. Acidotic changes in the umbilical artery were the sensitive indicators of uteroplacental insufficiency.

Small studies are available related to prophylactic phenylephrine infusion for the treatment of hypotension following spinal anesthesia. Hence, the study aims to determine the efficacy of prophylactic Phenylephrine on the incidence of hypotension in patients receiving a subarachnoid block for cesarean sections and assess the prophylactic effect of Phenylephrine on maternal hemodynamics and its consequences. The primary outcome measure was the assessment of prophylactic Phenylephrine on maternal hemodynamics (hypotension, nausea, and vomiting). In contrast, the secondary outcome was to assess the effect of prophylactic Phenylephrine on neonatal umbilical cord blood pH, umbilical blood artery pH, and Apgar scores at 1 and 5 minutes and fetal measures.

Methods

A prospective, randomized, open-label, controlled hospital-based observational study was conducted at Govt. District Headquarters Hospital and Apollo Institute of Medical Science and Research, Chittoor, AP, under PPP Mode Medical College, Chittoor, AP.

The hospital ethical committee approved the study protocol. Written informed consent was taken from 50 pregnant women from the American Society of Anesthesiologists (ASA) grade II (woman with uncomplicated pregnancy assigned ASA grade II) who were scheduled for elective Caesarean section during the study period under spinal anesthesia. Phenylephrine (Phenylephrine Hydrochloride Injection, Neon Laboratories Ltd. Mumbai, India) was used. For randomization, patients were distributed into two groups based on the random sampling method.

Inclusion criteria are singleton full-term pregnant women, age 20- 35yrs of ASA grade II. Scheduled for elective cesarean and the age group 20-35 yrs is selected for the study because of commoner age groups in this region. Exclusion criteria are pregnant above 35yrs, patients below 20yrs, patients having resting blood pressure > 140/90mm of Hg, history of hypertension, preeclampsia/eclampsia, hyperthyroidism, Patients having co-existing neurological, cerebrovascular, cardiovascular, renal, metabolic, psychiatric disorder, Patients with glaucoma, occlusive vascular disorder, History of Hypersensitivity to local anesthetics and any contraindications to spinal anesthesia.

Patients and drug allocation: Group A patients received intravenous prophylactic phenylephrine infusion at 100µg/min for 3min after completion of intrathecal injection. Then each min SAP was measured and infusion stopped if SAP > baseline and continued. Intravenous phenylephrine bolus 100µg was given when SAP is decreased to < 80% of baseline. Group B patients received intravenous

phenylephrine bolus 100µg when SAP is decreased to < 80% of baseline.

On arrival to the operation theatre, heart rate (ECG), blood pressure (non-invasive BP), respiratory rate, hemodynamics, and vitals were monitored.

HR, SBP, and DPB every minute after spinal anesthesia induction to the baby's extraction, the incidence of adverse hemodynamic effects, the incidence of nausea and vomiting, Umbilical artery blood pH, APGAR score at one and 5minutes.

All parturients were premedicated with injection ranitidine 50mg intravenously one hour before surgery.

After premedication, patients were allowed to rest undisturbed for several minutes, during which SAP was measured every 1-2 min. This was continued until measurements became consistent. Baseline SAP, DAP, and HR were taken as the mean of the two recordings. In the operation theatre, baseline vital signs were recorded using Multiparameter Monitor. Patients preloaded with ringer lactate solution, 10ml/kg over 15minutes after securing intravenous line with 18 gauze cannula and continued at 10 mL/min.

Spinal anesthesia-induced with patients in the lateral position: After skin infiltration with lidocaine, a 23-gauge Quinche Babcock needle was inserted at L2-3 or L3-4vertebral interspace, and the hyperbaric 0.5% bupivacaine 2.0 mL was injected intrathecally. SAP was measured at 1-min intervals beginning 1 min after spinal injection.

Immediately after the completion of the intrathecal injection, phenylephrine infusion was started in group A patients at 1 mL/min (100 µg/min), whereas group B patients did not receive it. Infusions were administered with a syringe pump connected to the intravenous line and continued for a minimum of 3 minutes, then the infusion was either stopped or continued according to the protocol based on the SAP measurement at each minute.

After intrathecal injection of bupivacaine, the upper sensory level of anesthesia was measured by assessing loss of pinprick discrimination. After 1 minute of spinal anesthesia; HR, SAP, and DBP were recorded every minute till the extraction of the baby. The dosing regimens of Phenylephrine were selected based on literature (10,11,23).

After delivery, oxytocin 20 IU in 1000ml saline was given by slow intravenous infusion. APGAR scores were assessed 1 and 5 min after delivery. Umbilical artery blood was taken from a double-clamped segment of the umbilical cord for immediate blood gas analysis.

Statistics: The observations are expressed as Mean±standard deviation. The baseline hemodynamic values and the postspinal hemodynamic changes at various time intervals were compared using the unpaired "t" test. Chi-square and Fischer Exact test have been used to find the significance of study parameters. A "P-value of ≤ 0.05" was considered to be statistically significant.

Results

The age of the patients ranged from 20-30 years. The mean age in group A was 25.8400 (SD 2.89) years, in group B was 25.04 (SD 2.28) years. The weight of the patients ranged from 55-75 kgs. In group A, the mean weight was 64.20 (SD 5.63), in group B was 64.88 (SD 2.33) kg. The height of the patients ranged from 150-168cms. The mean height in group A was 157.72 (SD4.83), in group B was 155. 68 (SD 2.64) cm. The level of a sensory block obtained was comparable in both the groups and most of the patients had an average blockade level of T6. The mean maternal heart rates range in groups A and B were 86.96 -95.00 bpm, 90.08-95.00, respectively. The heart rate was significantly lower in the infusion group in the 1^{st}, 2^{nd}, $10^{th,}$ and 11^{th} minutes.

SBP Variations: The mean systolic blood pressure variations in group A and group B after spinal anesthesia were 123.00- 128.47 mm Hg and 98.44-126.84 mm Hg, respectively. Both the groups had similar preinduction SBP; however, after spinal anesthesia, the mean systolic blood pressure was higher in the infusion group and was statistically significant (Table 2).

Table 1: Patient demographics.

	Group A		**Group B**		**P-value**
	Mean(bpm)	**SD**	**Mean(bpm)**	**SD**	
Baseline heart rate	90.6400	7.14656	92.3200	3.77183	0.304
1 min post anesthesia	89.3600	7.82560	94.4000	5.14782	0.01*
2 min post anesthesia	89.7600	7.55690	94.1600	5.79281	0.025
3 min post anesthesia	90.4400	6.89251	91.3200	4.67012	0.61
4 min post anesthesia	88.8000	7.25718	91.1600	3.84794	0.152
5 min post anesthesia	88.2000	5.67891	90.3200	6.28967	0.217
6 min post anesthesia	86.9600	7.12086	90.0800	4.60905	0.072
7 min post anesthesia	88.1600	6.49153	90.4800	3.52515	0.125
8 min post anesthesia	87.6400	6.74463	90.9600	5.67509	0.066
9 min post anesthesia	87.4783	8.52733	91.4167	6.06427	0.077
10 min post anesthesia	87.0588	8.19657	93.3158	5.91657	0.012*
11 min post anesthesia	87.5000	5.68038	94.6364	2.41962	<0.001**
12 min post anesthesia	93.0000	4.08248	94.0000	2.00000	0.4121
13 min post-anesthesia	95.5000	3.53553	95.0000	-	0.8741

The chi-square test, *significant; **highly significant; if the p value is >0.05, not significant.

DBP Variations: The mean diastolic blood pressure variations in group A and group B after spinal anesthesia were 72.7600-81.0000 mm Hg and 63.4800- 74.2400 mm Hg, respectively.

Both the groups had similar pre-induction DBP; however, after SPINAL ANAESTHESIA the mean diastolic blood pressure was higher in the infusion group and was statistically significant.

Mean blood pressure variations: The variations in mean Mean blood pressure in group A, group B after spinal anesthesia was in the range of 89.6000 -95.0000 mm Hg, 76.4000-91.7600 mm Hg, respectively. Both the groups had similar preinduction MBP; however, after spinal anesthesia, the mean Mean blood pressure was higher in the infusion group and was statistically significant.

Incidence of hypotension: The incidence of hypotension in group A, group B was 1 (3.57%) and 25 (100%), respectively, and the number of episodes of hypotension in group A and group B was 2 and 54 episodes, respectively. It is considered to be statistically significant with a p-value of 0.0001.

In group A, there were two episodes of hypotension in 1 patient who required two boluses of Phenylephrine in addition to the infusion for the correction of hypotension. In group B, all 25 patients had episodes of hypotension which required treatment with bolus doses of Phenylephrine.

Complications: There were no incidences of complications such as nausea and vomiting after induction of spinal anesthesia.

APGAR Score: The mean value of APGAR score at 5 min in groups A and B was 8.84±0.80 and 9.12±0.66, respectively, showing no significant difference between them. The mean value of APGAR score at 5 min in group A and group B were 9.68±0.47 and 9.80±0.40, respectively, and showed no significant difference between the two groups (Table 5).

Table 2: Comparison of SBP (mm Hg) between two groups.

	Group A		Group B		P value
	Mean	**SD**	**Mean**	**SD**	
Baseline	123.3600	8.58235	124.2400	6.67882	0.688
1 min post anesthesia	125.2000	8.18026	126.8400	9.89815	0.526
2 min post anesthesia	123.8400	10.07340	116.8400	13.00538	0.039
3 min post anesthesia	125.5200	7.78417	103.0800	12.87413	0.000*
4 min post anesthesia	124.4000	7.92675	98.4400	10.63046	0.000*
5 min post anesthesia	124.4000	9.90791	101.0000	10.88577	0.000*
6 min post anesthesia	123.3200	10.72272	103.6800	8.81627	0.000*
7 min post anesthesia	126.2800	9.87218	108.3200	8.77363	0.000*
8 min post anesthesia	125.9200	6.74463	109.5200	8.79924	0.000*
9 min post anesthesia	125.3182	11.38665	109.3333	7.08131	0.000*
10 min post anesthesia	128.4706	4.73178	109.7895	9.36055	0.000*
11 min post anesthesia	128.4000	6.80126	110.0000	8.63713	0.000*
12 min post anesthesia	127.0000	8.98146	109.4000	7.79744	0.005*
13 min post anesthesia	123.0000	4.24264	100.0000	8.2556	0.141

The chi-square test, *significant; if the p-value is >0.05, not significant.

Discussion

Phenylephrine was used for all the patients, and no other drug was given intraoperatively before extraction of the baby. This makes the possibility of influences of other drugs on our study drug remote. All the patients had similar demographic parameters in our study group, which made their influence very unlikely.

Following spinal anesthesia for Caesarean section, hypotension remains a major drawback, with an incidence of up to 85% reported in the literature. This is despite pregnant patients having 40-50% of more blood volume at term than nonpregnant patients. Pregnants at term are more prone to develop hypotension due to the occurrence of aortocaval compression by the fetal head and a higher level of sympathetic blockade owing to increased spread of local anesthetic in the cerebrospinal fluid (12). Hypotension, hazardous to the mother and more so, is better prevented than treated to the fetus. Blood pressure is usually maintained in the face of vasodilation, caused due to factors other than central neural blockade, by a reflexive increase in cardiac output. However, in the presence of spinal-induced venodilation, venous return is reduced to the extent that cardiac output cannot increase and is often reduced. The result is severe hypotension with reduced uteroplacental perfusion and APGAR score.

The current study compares prophylactic infusion of Phenylephrine and a control group not receiving the infusion to prevent hypotension during spinal anesthesia for cesarean section. However, both the groups received a bolus dose of phenylephrine 100µg intravenous to treat any episodes of hypotension.

Table 3: Comparison of DBP (mm Hg) between two groups.

Study period	Group A		Group B		P-value
	Mean	SD	Mean	SD	
Baseline DBP	74.5200	4.69148	72.2800	4.37340	0.087
1 min post anesthesia	75.4800	6.47508	74.2400	5.87566	0.4605
2 min post anesthesia	74.2400	6.58458	71.7200	5.87026	0.1628
3 min post anesthesia	74.6400	5.36097	67.4800	6.15169	<0.0001**
4 min post anesthesia	73.8000	8.54888	65.4000	6.87386	0.0004*
5 min post anesthesia	73.6400	7.89979	63.4800	14.19542	0.0031*
6 min post anesthesia	72.7600	8.08435	67.0400	5.55638	0.0048*
7 min post anesthesia	72.8800	6.99595	69.0000	6.95821	0.0537
8 min post anesthesia	73.8800	6.95414	68.7600	4.71946	0.0039*
9 min post anesthesia	73.6522	8.13303	68.6250	3.92110	0.0069*
10 min post anesthesia	75.5882	4.95049	67.8947	7.40041	0.0001*
11 min post anesthesia	76.1333	5.54033	70.9091	3.14498	0.0101*
12 min post anesthesia	78.2857	6.34335	70.0000	1.58114	0.0177*
13 min post-anesthesia	81.0000	2.82843	72.0000	-	0.1388

The chi-square test, *significant; **highly significant; if the p value is >0.05, not significant.

Effect on maternal hemodynamics: The study observed that during the initial part of the study at 1-2 minutes and later part of the study from 10th to 11th minute, the heart rate was higher in the group B patients compared to that of group A. This is probably due to reflex bradycardia caused by the phenylephrine infusion in group A which lowered the heart rate. However, between the 3rd and 9th minute, the heart rate was comparable in both the groups. This was because of the phenylephrine boluses given to the patients in group B to treat the hypotension episodes, which caused reflex bradycardia. However, none of the

Table 5: Usage of Phenylephrine: Intravenous Fluids, Duration from Skin Incision to Delivery of Baby Umbilical Artery Blood pH.

	Group A	Group B	P value
Usage of Phenylephrine	496 ±280.59	216 ±94.33	0.0001*
Intravenous Fluids(ml)	105.60 ± 14.74	104.00±12.24	0.678
Duration from Skin Incision to delivery of baby(Sec)	532.8±60.17	530.4±59.19	0.89
Umbilical artery blood pH	7.1736±0.03121	7.1756±.02740	0.811
APGAR score @1 minute	8.84±0.80	9.12±0.66	0.185
APGAR score @5 minute	9.68±0.47	9.80±0.40	0.344

The chi-square test, *significant; if the p-value is >0.05, not significant.

patients require treatment with atropine in both groups. These findings suggest infusion keeps the heart rate uniformly but on a lower side than the boluses where a fluctuation in the heart rate was observed.

The current study results correlate with the recent study by Joo Yeon Jeon et al. and Patel et al. (13, 14).

Sharma et al. found that the mean heart rate decreased significantly after administration of phenylephrine boluses whereas it remained high in the patients receiving mephentermine (15). Also, Thomas et al. found that more than 50% of women given Phenylephrine developed significant bradycardia compared to the ephedrine group (5). As the cardiac output is the heart rate and stroke volume product, this suggests that Phenylephrine restored a greater stroke volume than Ephedrine. Because Phenylephrine is virtually devoid of β-inotropic effect, the better stroke volume produced by Phenylephrine probably reflects better preload than Ephedrine (14). Nevertheless, in the ephedrine group, cardiac sympathetic denervation was masked by the chronotropic effect of this β adrenergic agonist. Hall et al. also recorded 2 cases of bradycardia in the phenylephrine group, which was less than 40beats/min, corrected with a bolus dose of atropine (16). All these episodes occurred after multiple doses of Phenylephrine, and no patients developed bradycardia. The findings of Patel et al. were consistent with our study and suggest that Phenylephrine causes reflex bradycardia (14).

Blood pressure: In our study, we also observed that hypotension incidence is 3.57% (n=1/25) in group A and 100% in group B. It was observed that the incidence of hypotension was higher in group B. This reflects that more stable management of blood pressure can be achieved by phenylephrine infusion as it uniformly maintains the plasma level of this vasopressor.

Our study observed that the difference in systolic blood pressure, diastolic blood pressure, and mean blood pressure was highly significant between the two groups.

The SBP, DBP, and mean blood pressure was consistently higher in Group A when compared to Group B. This probably was due to post-synaptic α receptors' stimulation by Phenylephrine, resulting in intense arterial and peripheral venoconstriction causing a rise in blood pressure.

However, we found that the required dose of Phenylephrine was much higher in the infusion group than in the control group. At term, the uterine vascular bed is maximally vasodilated and unable to autoregulate when perfusion pressure is reduced. Consequently, a higher adrenoceptor density renders uteroplacental blood flow potentially vulnerable to vasoconstriction induced by α adrenergic agonists. Indeed, infusion of Phenylephrine at 8µg/kg/min has been reported to decrease uteroplacental blood flow by 50% however, the relationship between phenylephrine dose and uterine vascular resistance is not linear and dramatic increases in Uterine vascular resistance seen only to appear with doses greater than 100µg/min thus, the satisfactory fetal outcome in human studies may reflect the lower doses used. This is consistent with our study, where the infusion rate was 100µg/min.

Non-hemodynamic side effects: In our study, no patient developed nausea or vomiting (who received Phenylephrine). Cooper et al. suggest that the possible explanation for nausea and vomiting is increased vagal tone following preload reduction (7). Cardiac preload decreased in spinal anesthesia, but phenylephrine, a pure α- agonist, provides better venoconstriction, reducing the cardiac preload and diminishing the vagal reflex (17). Sarvanan et al. found that Phenylephrine was significantly better among the patients with ineffective blood pressure control than Ephedrine in the prevention of vomiting (17).

According to our research, all the studies demonstrated a lower incidence of nausea and vomiting in patients receiving Phenylephrine (18, 19).

Neonatal outcome: The APGAR scores and measured umbilical artery blood pH were used to indicate the adequacy of placental perfusion. Despite periods of maternal hypotension in group B and decreased heart rate in group A, we found no significant difference in either APGAR score or umbilical artery blood pH between the two groups. This could be due to immediate correction of hypotension episodes and maintenance of uteroplacental perfusion in both groups.

The APGAR score was similar in the groups and

never less than 8, although the incidence of arterial pH < 7.18 was greater than desired. Several studies reported a surprisingly high incidence of acidosis (not accompanied by neonatal depression) after spinal anesthesia for cesarean deliveries (19, 20). Another mechanism for decreased uterine artery blood pH is by a prolonged period of decreased maternal cardiac output occurring before delivery. The results of our study demonstrate that the higher umbilical artery pH and the incidence of nausea and vomiting were null when Phenylephrine is titrated with aim of maintaining the maternal BP at 100% of a baseline compared with <90% or <80% baseline. Robson et al. found that umbilical artery blood pH correlated well with maternal cardiac output (but not with BP itself) (21).

Also, Hall and coworkers found that despite periods of maternal hypotension, which occurred longer than 2 min, and periods of maternal bradycardia, there was no significant difference in either APGAR scores or blood-gas data between the three groups (16). Joupilla et al. also showed that intravenous preload maintains placental blood flow despite moderate maternal pressure reduction, thus minimizing fetal acidosis. Our study is taken precautions by preloading the patientswith10ml/kg of Ringer lactate solution, which probably would have maintained placental blood flow during hypotensive episodes lasting longer than 2minutes (22). Recent studies have also shown that Phenylephrine in bolus or infusion has no adverse neonatal effects (16, 17, 23).

Conclusion

Prophylactic phenylephrine infusion is superior for the control of hemodynamics. When given as a prophylactic infusion, the results suggest that Phenylephrine leads to significantly the best control of post-spinal hypotension during c-section with no maternal side effects. The APGAR scores and fetal acid-base status did not show any evidence of acidosis, which was similar. The prophylactic phenylephrine infusion is the simple method for managing better fetal and neonatal measurements without variating the outcomes.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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