

Intravenous Bolus Doses of Phenylephrine Vs Ephedrine Along with Crystalloid Co-Loading in the Prevention of Hypotension during Spinal Anesthesia for Caesarean Section: A Randomized Comparative Study

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Abstract

Aim: The objective of the present study was to compare the vasopressor effects of ephedrine and phenylephrine in ameliorating hypotension in elective caesarean delivery receiving crystalloid co-loading, during intrathecal bupivacaine injection.

Methods: The present study was conducted in the Department of Anesthesia, Sadar Hospital Muzaffarpur, Bihar, India for 1 year and one hundred and twenty parturients of ASA (American Society of Anesthesiologist)-I and II, weighing 50-80kgs, of height 140-170 cms, having a singleton normal pregnancy more than 36 weeks of gestation, with indications for caesarean section under spinal anesthesia were taken for this study.

Results: The patients' characteristics like age, height, weight and ASA were similar and no significant difference was observed between the groups. The difference observed in baseline heart rate, systolic, diastolic, and mean blood pressures between two groups was statistically insignificant. There was higher incidence of bradycardia in patients receiving phenylephrine than those receiving ephedrine. The difference in mean heart rate till delivery compared between two groups immediately after spinal anesthesia, at 2, 4, 6, 8, 10, and 12 minutes was significant while it was insignificant at 0 and 14 minutes (P value < 0.05: significant). The difference in mean heart rate compared between two groups at delivery, 5, 10, minutes and at the end of the surgery was insignificant except at delivery and 15 minutes after delivery (P value < 0.05: significant).

Conclusion: We concluded from this study that phenylephrine and ephedrine are equally efficient in managing hypotension during spinal anesthesia for elective cesarean delivery. There was no difference between two vasopressors in the incidence of true fetal acidosis. Neonatal outcome remains equally good in both the groups.

Keywords: Hypotension, Ephedrine, Phenylephrine, Spinal anesthesia

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Introduction

Spinal anesthesia has been widely used for cesarean section and has been found

efficacious and safe. The incidence of hypotension during cesarean section under

spinal anesthesia has been reported to be 80–90% or greater depending on the definition used. [1,2] For the mother, hypotension is especially associated with nausea and vomiting [3] and in more severe cases there may be risk of decreased consciousness, pulmonary aspiration, respiratory depression, and cardiac arrest. Hypotension can have detrimental effects on neonate, which include decrease in utero-placental flow, impaired fetal oxygenation with asphyxial stress, and fetal acidosis. [4]

Because hypotension may be associated with both maternal and neonatal morbidity, many different methods have been investigated alone and in combination for both its prevention¹ and treatment. Left uterine displacement is known to decrease the effects of aortocaval compression. [5] Leg elevation alone has not been shown to reduce the incidence of hypotension. [6] Prehydration or preloading is commonly administered but it has controversial results. [7,8] Because of the poor efficacy of nonpharmacological techniques to effectively manage hypotension, a vasopressor is usually required during spinal anesthesia for cesarean section. In choosing an appropriate vasopressor in obstetrics, a number of factors like efficacy for maintaining blood pressure, non-cardiovascular maternal effects, ease of use, direct and indirect fetal effects, cost, and availability need to be considered. Cesarean section is the earliest obstetrical operation and till today remains the only method by which babies are delivered when the normal delivery fails. It is commonly accepted that serious trauma to the baby can be eliminated by avoiding potentially difficult mid forceps or vaginal breech deliveries by performing a caesarean section.

Vasopressor used commonly for preventing hypotension during spinal anesthesia are ephedrine, phenylephrine,

and metaraminol. Use of ephedrine in obstetric patients is supported by animal studies, which showed that uteroplacental blood flow is better maintained when ephedrine was used to raise maternal blood pressure. [9] Disadvantages of ephedrine include a slow onset and relatively long duration, which may make accurate titration of blood pressure difficult. [10]

Phenylephrine is a potent direct-acting alpha agonist. In pregnancy, because of a generalized reduction in pressor response to endogenous and exogenous vasoconstrictors, [11] relatively large doses of phenylephrine may be required. However, fetal acidosis has not been demonstrated when phenylephrine is used liberally to maintain maternal blood pressure and prevent symptoms. [12]

The objective of the present study was to compare the vasopressor effects of ephedrine and phenylephrine in ameliorating hypotension in elective caesarean delivery receiving crystalloid co-loading, during intrathecal bupivacaine injection.

Materials and Methods

The present study was conducted in the Department of Anesthesia, Sadar Hospital Muzaffarpur, Bihar, India for one year and one hundred and twenty parturients of ASA (American Society of Anesthesiologist) – I and II, weighing 50-80kgs, of height 140-170cms, having a singleton normal pregnancy more than 36 weeks of gestation, with indications for caesarean section under spinal anesthesia were taken for this study.

Parturients with hypertension, diabetes mellitus, and impairment of cardiovascular or cerebrovascular function, and contraindications to spinal anaesthesia were excluded from the study.

After obtaining written informed consents, the participants were divided randomly into two groups (n=50 in each) using

computer generated randomization method. All were co-loaded with rapid administration of Ringer's Lactate solution at the dose of 20 ml/kg once cerebrospinal fluid was confirmed.

The groups were divided as follows:-

Group E (n = 60): Parturient in Group E to receive 6 mg of intravenous bolus Ephedrine

Group P (n = 60): Parturient in Group P to receive 100 µg of intravenous bolus Phenylephrine.

On the previous day of operation, the participants were examined for pre-anesthetic fitness. Patients with comorbidities such as hypertension, diabetes mellitus, bronchial asthma, impaired liver or renal function, coagulopathy, cardiovascular disease were excluded from the study. Pre-anesthetic medication which included ranitidine 150 mg was administered on the night before the day of surgery. As in all other surgeries, intravenous line was set with 18G cannula in the non-dominant hand. In order to maintain patency of cannula, intravenous fluid with isotonic saline was started. For study participants, pre-anesthetic medication of metoclopramide 10 mg and ranitidine 50 mg was given through intravenous route 20 mins prior to the surgery. Before being transferred to operation theatre, baseline parameters were recorded and monitored 10 – 20 min after arrival from the ward for heart rate, systolic and diastolic blood pressure in sitting posture and oxygen saturation in pre anesthetic room. After reaching the operation theatre, the parturients were observed with electrocardiogram (ECG), non-invasive arterial blood pressure (NIBP) and oxygen saturation (SpO₂) by pulse oximetry with the monitor 'Clarity Smart' till the end of the procedure. Baseline, parameters such as oxygen saturation, heart rate, systolic and diastolic blood pressure was recorded. The L3-

L4interspace was used for spinal anesthesia keeping the patient in left lateral using the midline approach. Sterile precaution was maintained throughout the procedure. The Quinke's needle 25G was used and dural puncture was established by the identification of cerebrospinal fluid. Once the plane of injection is established, Bupivacaine at the dose of 2 ml (10 mg) of 0.5% solution was injected at the rate of 0.2 ml/sec. Co-loading with rapid administration of 20 ml/kg Ringer lactate solution started simultaneously after identification of the cerebrospinal fluid with intrathecal injection. Immediately after the administration of the anesthetic agent, the parturients shifted to supine position with the operation table in horizontal plane to make the level of block upto T6–T4. During the initial 5 minutes of surgery the parameters such as oxygen saturation, blood pressure and pulse rate recorded for every one minute followed by every five minutes until the completion of the surgery.

The study population was randomized using computer generated randomization into two groups, group E (Ephedrine) and group P (Phenylephrine) to receive either ephedrine 6 mg intravenous bolus or phenylephrine 100 µg intravenous bolus when there is an episode of hypotension (fall in systolic blood pressure more than 20% from the baseline) in two consecutive readings. No vasopressors were given to normotensive patients. Total dose of vasopressor used in a hypotensive patients were recorded. When the patient developed bradycardia with heart rate less than Glycopyrolate 0.2 mg i.v was administered. On delivery of the baby, after clamping the umbilical cord, the umbilical cord blood was taken in a heparinized syringe and sent for analysis for pH and Apgar score was recorded at 0,1 & 5 minutes for fetal well-being. Once baby is delivered, injection oxytocin was infused in normal saline along with

injection methylephedrine 0.2mg in divided dose through intramuscular and intravenous route. Baseline hemodynamic parameters, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, fall of > 20% systolic blood pressure from baseline value, bradycardia, intraoperative nausea and vomiting, block height, ephedrine and

phenylephrine requirements intra operatively, Apgar score of the baby and the umbilical cord blood pH were all monitored and recorded. Chi-square test was used for comparing the categorical variable and Student T-test for continuous variables and $p \leq 0.05$ was considered significant.

Results

Table 1: Demographic profile of the study participants

Parameters	Group E (n=60)	Group P (n=60)	Degree of freedom	P value & Inference
Age in years (mean±SD)	26.5±2.25	27.7±2.1	98	0.65
Weight in Kgs (mean±SD)	61.9±5.25	71.4±6.97	98	0.32
Height in Cms (mean±SD)	160.4±5.58	157.6±4.81	98	0.30
ASA (I:II)	39:1	36:4	1	0.36

The patients' characteristics like age, height, weight and ASA were similar and no significant difference was observed between the groups.

Table 2: Comparison of baseline heart rate, systolic, diastolic and mean blood pressure in groups E and P

Characteristics	Group E Mean±SD	Group P Mean±SD	t-value	P-value
Heart rate	90.32±16.65	87.38±13.03	1.01	0.320
Systolic blood pressure	120.24±12.35	120.44±9.84	0.95	0.920
Diastolic blood pressure	78.32±9.90	76.16±9.30	1.03	0.306
Mean blood pressure	90.30±10.07	92.92±8.85	0.62	0.450

The difference observed in baseline heart rate, systolic, diastolic, and mean blood pressures between two groups was statistically insignificant.

Table 3: Comparison of heart rate, systolic and diastolic blood pressure between groups E and P before delivery

Parameter till delivery	Heart rate (bpm)			Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
	Group E Mean±SD	Group P Mean±SD	P value	Group E Mean±SD	Group P Mean±SD	P value	Group E Mean±SD	Group P Mean±SD	P value
Immediately after SA	92.40 ±21.45	86.02 ±12.02	0.070	107.88 ±14.87	107.30 ±13.57	0.843	69.66 ±11.79	69.80 ±10.50	0.948
2 min	99.8 ±22.38	84.52 ±17.86	0.001	119.76 ±17.44	110.12 ±17.44	0.071	77.52 ±11.76	73.04 ±12.85	0.055
4 min	99.78 ±21.37	82.88 ±16.90	0.001	112.20 ±18.05	107.60 ±17.96	0.089	73.56 ±11.16	74.16 ±10.67	0.770
6 min	91.80 ±15.07	82.28 ±16.20	0.004	108.52 ±20.21	105.96 ±16.87	0.500	74.84 ±13.19	76.12 ±12.58	0.634
8 min	93.40	85.80	0.021	110.96	106.56	0.079	74.68	73.20	0.512

	±15.22	±17.33		±14.31	±14.92		±11.66	±11.60	
10 min	90.86 ±15.07	4.28 ±15.20	0.038	109.84 ±10.49	105.76 ±14.58	0.093	77.16 ±11.19	75.88 ±9.50	0.528
12 min	91.62 ±15.83	85.44 ±15.35	0.056	13.96 ±12.46	109.56± 10.42	0.075	75.52 ±8.22	76.12 ±8.32	0.622
14 min	97.00 ±3.93	94.20 ±5.12	0.215	115.7 ±5.68	115.20 ±5.02	0.093	72.67 ±11.36	72.00 ±14.24	0.929

Table 4: Comparison of heart rate, systolic and diastolic blood pressure between groups E and P after delivery

Parameter till delivery	Heart rate (bpm)			Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
	Group E Mean±SD	Group P Mean±SD	P value	Group E Mean±SD	Group P Mean±SD	P value	Group E Mean±SD	Group P Mean±SD	P value
At delivery	97.40 ±13.42	91.76 ±14.00	0.03	116.92 ±14.60	120.68 ±12.32	0.22	75.96 ±11.75	77.72 ±9.72	0.45
5 min	93.94 ±14.82	88.72 ±13.23	0.09	113.56 ±15.35	112.48 ±14.06	0.70	74.12 ±11.41	74.76 ±10	0.75
10 min	88.26 ±13.18	86.24± 12.23	0.45	116.84 ±17.43	112.52 ±17.05	0.26	76.88± 12.45	72.98 ±11.29	0.09
15 min	93.62 ±8.84	91.63 ±15.17	0.00	116.04 ±14.55	114.40 ±14.86	0.54	75.80± 8.02	73.12 ±9.57	0.09
20 min	90.69 ±5.52	91.80 ±7.56	0.94	116.00 ±8.26	104.67 ±19.66	0.08	71.23 ±8.12	68.91 ±10.40	0.40
End of surgery	91.12 ±6.90	85.88 ±12.98	0.22	115.00 ±13.54	114.72 ±12.74	0.90	75.04 ±9.28	72.64 ±7.78	0.17

There was higher incidence of bradycardia in patients receiving phenylephrine than those receiving ephedrine. The difference in mean heart rate till delivery compared between two groups immediately after spinal anesthesia, at 2, 4, 6, 8, 10, and 12 minutes was significant while it was

insignificant at 0 and 14 minutes (P value < 0.05: significant). The difference in mean heart rate compared between two groups at delivery, 5, 10, minutes and at the end of the surgery was insignificant except at delivery and 15 minutes after delivery (P value < 0.05: significant).

Table 5: Apgar score of the children born at birth, 1 min and 5 mins of delivery

Time points	Group E	Group P	p value
At birth	7.44±0.5	7.38±0.5	0.8
1 min	8.52±0.7	8.64±0.6	0.24
5 mins	8.7±0.6	8.64	0.1

Apgar score of the children born at birth, 1 min and 5 mins in both the groups did not predict any significant statistical difference.

Discussion

In our study, the insignificant variations in the weight, height, age as well as ASA status of the parturients between the groups, emphasize the fact that the present study was made blind on the weight,

height, age and ASA of the parturients. In other words, parturients considered for our study who received ephedrine 6mg or phenylephrine 100 mcg were more or less similar as regards their age, weight, and height and ASA status on the study of comparison of the two drugs. In our study, the incidence of hypotension was 42% in both group E and group P without any statistical difference when we used crystalloid co-loading. MKhan et al. observed a difference ($p < 0.0008$) in hypotension incidence between coload (44%) and preload (70%) groups which is comparable with the present study. [13]

In this trial 60 patients undergoing caesarean section were randomized to receive 20 mL/kg Ringer lactate solution IV either by coload or preloading (20 min before the anesthesia). The incidence of hypotension was significantly decreased in the coload versus preload group (36% vs 60%) and ephedrine requirements before delivery were also reduced (median: 0 vs 10 mg). A slightly different design was followed in a study conducted by NganKee et al where the authors compared coload with no fluid with infusion of phenylephrine in both groups. [14]

In this study, there was higher incidence of bradycardia in patients receiving phenylephrine than those receiving ephedrine. This was expected to be due to increase in blood pressure with an α -agonist may lead to reactive bradycardia (baroreceptor reflex). The results of this study were in accordance with the study of Lee et al. [4] in which they reported higher incidence of bradycardia in patients receiving phenylephrine as compared with patients receiving ephedrine for prevention of hypotension during spinal anesthesia for cesarean section.

We confirmed in this study that there was no difference between ephedrine and phenylephrine in their efficacy for managing hypotension following spinal

anesthesia in parturients undergoing cesarean delivery in the range of doses that have been studied. The results of this study are in accordance with the study of Adigun et al. [15] They observed that both vasopressors effectively restored both the systolic and diastolic blood pressure. They also concluded that phenylephrine is safe and can be used as effectively as ephedrine. Gunda et al. [16] compared the effectiveness and the side effects of vasopressors, ephedrine, and phenylephrine, administered for hypotension during elective cesarean section under spinal anesthesia. They found that for the management of hypotension there was no difference, similar to our findings. However, the study suggests that phenylephrine may be more appropriate vasopressor when considering maternal well-being. This may have been because less dose of ephedrine was used in this study as compared with this study. This study was not consistent with the work of Magalhães et al. [17] study on ephedrine versus phenylephrine for prevention of hypotension during spinal block for cesarean section and effects on fetus. They concluded that ephedrine was more effective than phenylephrine in the prevention of hypotension. This may have been because less dose of phenylephrine was used in their study as compared with this study.

In both the group, heart rate was kept near baseline value until the induction of anesthesia after which heart rate increased significantly for about ten minutes parallel to interval of fall in mean arterial pressure. Following which the heart rate was back to base line values in both the group. Heart rate was similar in ephedrine group and the phenylephrine group at all measured intervals. However, at 4 to 5 minutes interval, the heart rate was at the range of 95-100 beats per minute in group E and 100-105 beats per minute in group P, which were statistically significant though

clinically not significant. Similar findings were found by M Khan et al. [13] who observed heart rate changes with increased trend for around ten minutes. This change was attributed to causes like anxiety, aortocaval compression and hypotension.

The difference in the incidence of hypotension between the groups was statistically not significant. The difference in systolic blood pressure between two groups after delivery at all times except at 2, 3 minutes was statistically insignificant. At the 2 minute, the range of systolic blood pressure in two groups was 98-102 mmHg, 3 minutes systolic blood pressure was 90-95 mmHg. The difference in diastolic blood pressure between two groups after delivery at all times except at 2, 4 minutes was statistically insignificant, at 2 mins the diastolic blood pressure was 54-63 mmHg and at 4 minutes diastolic blood pressure was 50-55 mmHg. The difference in mean blood pressure between two groups after delivery at all times except at 2 minutes was statistically insignificant ($P>0.05$), at 2 minutes mean blood pressure was 70-75 mmHg ($P=0.03$). These findings were in accordance with the results of the studies conducted by M Khan et al and Nazir I et al. [13,18].

However, this study showed that women who received phenylephrine had neonates with higher umbilical cord pH than women who received ephedrine, although the risk of true fetal acidosis (umbilical artery pH<7.20) was similar. No neonate in both groups had pH < 7.2. Prakash et al. [2] found that women who were given phenylephrine had neonates with higher umbilical arterial pH values than those given ephedrine. There was no difference between two groups in the incidence of true fetal acidosis similar to this study finding. Cooper et al.[19] concluded in their study that the umbilical artery pH was similar, whether ephedrine or phenylephrine was used to maintain

maternal arterial pressure, which is consistent with this study. Acidotic changes in umbilical artery are sensitive indicators of uteroplacental insufficiency. The study finding is indirect evidence that uterine blood flow may in fact be better with phenylephrine compared with ephedrine. There was no difference in Apgar score between the two groups. In this study, no neonate had an Apgar score < 7 at 1 or at 5 minutes. The difference in birth weight of neonates between two groups was statistically nonsignificant. [19]

Conclusion

We concluded from this study that phenylephrine and ephedrine are equally efficient in managing hypotension during spinal anesthesia for elective cesarean delivery. There was no difference between two vasopressors in the incidence of true fetal acidosis. Neonatal outcome remains equally good in both the groups.

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