COMPARATIVE STUDY OF PHENYLEPHRINE AND EPHEDRINE IN CONTROLLING HYPOTENSION IN PREGNANT PATIENTS UNDERGOING CAESAREAN SECTION UNDER SPINAL ANAESTHESIA

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ABSTRACT

BACKGROUND

A vasopressor drug is often required to control hypotension. Many authors have compared ephedrine and phenylephrine as vasopressor in patients undergoing elective cesarean section with conflicting conclusions, but none have evaluated these two agents in patients from the North-Eastern part of India. As a secondary objective, we intended to evaluate the side effects and umbilical artery blood pH (UApH).

MATERIALS AND METHODS

Term parturients of ASA-I and ASA-II category, in the age group of 20-30 years, with weight of 50-70 kg and height of 150-170 cms posted for elective caesarean section under spinal anaesthesia were selected for the study. After dural puncture with a 23G spinal needle, 2.5 ml of 0.5% bupivacaine heavy was injected. Systolic and diastolic blood pressures (SBP and DBP) were recorded after subarachnoid block, and then every 2 mins for next 20 mins and thereafter every 5 mins till 30 minutes. Whenever the SBP falls below 20% of the baseline value, the study drug was given. Rescue atropine sulphate (0.3 mg IV) was given when the heart rate became less than 50.

RESULTS

The number of boluses of phenylephrine(Group-P) required to maintain maternal blood pressure were less as compared to Ephedrine(Group- E) in the first 6 minutes. In Group-P, 23.33% patients required single dose of Atropine to treat bradycardia and 76.67% patients did not require any atropine dose. In Group- E, no patients required any rescue dose of Atropine. Higher UApH in Group-P (Mean 7.37±0.023) as compared to Group-E (7.319±0.021) was noticed.

CONCLUSION

The maternal blood pressure was better maintained with phenylephrine as compared to ephedrine. There was less maternal heart rate along with statistically significant higher UApH in the patients receiving phenylephrine.

KEYWORDS

Hypotension, Phenylephrine, Ephedrine, Caesarean, Spinal Anaesthesia.

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BACKGROUND

Hypotension is a common complication of spinal anaesthesia with various ill-effects on both mother as well as the neonate. The side effects are maternal nausea, vomiting, dizziness and decreased consciousness as well as impaired fetal oxygenation leading to fetal acidosis.[1] There are various literatures describing methods of controlling hypotension in obstetric anesthesia. Despite the common measures like uterine displacement and IV fluid preloading, a vasopressor drug is often required.[1,2] Historically, ephedrine was recommended on the basis of observations in pregnant sheep that showed it was more effective in increasing arterial pressure with better preservation of uteroplacental blood flow compared with other vasopressors.[3] This was explained by ephedrine's predominant effect that caused an increase in arterial pressure by increasing cardiac output rather than by vasoconstriction. But its position has been challenged because of potential complications that include supraventricular tachycardia, tachyphylaxis and fetal acidosis.[4]

Phenylephrine, a pure alpha agonist maintains haemodynamics well. But the use of such pure alpha agonists have generally been avoided because of concerns about their potential adverse effect on uterine blood flow.[1] A recent meta- analysis questioned this long held belief.[5] Recent evidence suggests that phenylephrine may be a better choice.[6] Many authors have compared ephedrine and phenylephrine as vasopressor in patients undergoing elective cesarean section with conflicting conclusions.[7,8,9,10,11,12,13]

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But none have evaluated these two agents in patients from the North Eastern part of India. Moreover, many have used different drug delivery regimens.

Due to non-availability of facilities to use the drugs as infusions, this study was undertaken to primarily evaluate the efficacy of bolus of phenylephrine and ephedrine to control the adverse hemodynamic consequences in a patient undergoing caesarean section under spinal anaesthesia. As a secondary objective, we intended to evaluate the side effects and umbilical artery blood pH (UApH) in both the groups.

MATERIALS AND METHODS

This randomized clinical comparative study was conducted in the Department of Anaesthesiology and Critical Care at Gauhati Medical College and Hospital, with prior permission from the Hospital Ethical Committee and written informed consent from all the patients. Term parturients of ASA-I and ASA-II category, in the age group of 20-30 years, in the weight range of 50-70 kg and height of 150-170 cms posted for elective caesarean section under spinal anaesthesia were selected for the study. We excluded patients with any specific contraindication for spinal anaesthesia or any drugs to be used, infection over the proposed site of injection, any systemic disease or systemic infection and patients with communication problems.

Block randomization of variable sizes were carried out to have two groups of patients with 30 patients in each group. Allocation of concealment was achieved by use of opaque envelope that carried the group allocation information. The envelopes were opened just prior to performance of spinal anaesthesia. The patients, person preparing the drugs under evaluation, person collecting data were kept blinded to the group allocation.

We enrolled patients that met inclusion criteria and those that developed hypotension after institution of spinal anaesthesia were included in the study. Pre-anaesthetic checkup was done on the previous evening or any time before cesarean section as dictated by clinical circumstances. The patients were explained in detail about the operative procedure, anaesthetic technique and the postoperative monitoring. The patients and their guardians were properly counseled for their cooperation. Thirty minutes prior to stipulated time of surgery, all parturients were premedicated with Metoclopramide 10 mg and Ranitidine 50 mg intravenously (IV). Patient's electrocardiogram (ECG), peripheral oxygen saturation (SpO2), respiratory rate and non-invasive blood pressure (NIBP) was monitored and the average of the first three readings taken one minute apart was taken as the baseline values. A person who was not involved in any further process of the study prepared identical syringes that contained either 100 microgram/ml phenylephrine in a 5 ml syringe (Group P) or ephedrine 5 mg/ml in a 5 ml syringe (Group E). As per group assignment, the relevant syringe was handed over to the anaesthesiologist conducting the spinal anaesthesia. Unless contraindicated by clinical circumstances, peripheral IV access with an 18G cannula was obtained in the left dorsum of the hand. Preloading with Ringer's Lactate solution 20 ml / kg body weight was carried out. The patients were then put in sitting position near the edge of the table and a pillow was placed on the abdomen to support her hands while the assistant maintained normal flexed position. Skin in the lumbar spine area was prepared with antiseptic povidone iodine solution and allowed to dry. Projected area was covered with sterile cloth. After the readiness of equipment and local anesthetics, the midline spinal puncture was performed in the study. The lumbar puncture was done in L3-4 interspace. A subcutaneous skin wheal was developed overlying this space with 1 ml of 2.0% lignocaine. After dural puncture with a 23-gauge Quincke's spinal needle and confirming free flow of cerebrospinal fluid (CSF), 2.5 ml of 0.5% bupivacaine heavy was injected at the rate of approximately 0.2 ml/ sec. The patients were then returned to the supine position. A wedge was placed under the right hip for left uterine displacement. Oxygen was administered at a rate of 3L/min by a face mask to all the patients till the delivery of the baby. The level of loss to pinprick sensation was assessed and surgery was started when sensory loss of up to T6 was achieved. Systolic and diastolic arterial pressures (SBP and DBP) were recorded after subarachnoid block, and then every 2 mins for next 20 mins and thereafter every 5 mins till 30 minutes. Whenever the hypotension (fall in systolic pressure more than 20% of the baseline value) occurred, the study drug was given IV bolus. Rescue atropine sulphate (0.3 mg IV) was given when the heart rate became less than 50. Heart rate, both systolic and diastolic pressures were noted every 2 mins after the study drug was given. The numbers of boluses and time taken to develop hypotension were noted. Subarachnoid block-delivery and incisional delivery time were recorded. Umbilical arterial blood sample from a segment of umbilical cord after application of a double-clamp before the baby's first breath was sent immediately for pH estimation. Newborn infants were not studied beyond the immediate post delivery period. Sahu et al reported that 55% that received ephedrine needed two or more boluses.[2] To detect a decrease to 20%, a sample size of 27 patients in each group was required, using a type I error of 0.05 and a power of 0.80. To account for possible attrition, we intended to include 30 patients in each group. chi-square test was used to analyze categorical data e.g. ASA physical status and indication of caesarean section. Mean and standard deviations were computed for age, weight, height and APGAR score and analyzed by independent sample t-test, while primary outcome that is correcting hypotension was measured in proportion and percentage and analyzed by chi-square tests between the groups. A p-value ≤ 0.05 was accepted as statistically significant.

RESULTS

One hundred pregnant women meeting inclusion criteria was enrolled in the study, of which 60 patients developed hypotension and received the drugs under evaluation. Both the groups were comparable in terms of demographic profile and surgical parameters (Table 1).

Parameters	Group P		Group E		P Value
	Total Number (n) /Percentage (%)/Mean	SD	Total Number /Percentage/Mean		
ASA I ASA II (n)	25 5		24 6		0.739
Age (Years)	26.133	2.24	26.20	2.06	0.905
Height (Meters)	158.633	4.33	158.40	3.97	0.828
Weight (Kg)	60.70	4.96	61.4	4.73	0.578
SAB- Del (Sec)	524.50	102.87	565.90	137.71	0.192
UI-Del (Sec)	72.70	15.75	75.40	15.27	0.503

Table 1. Demographic and Surgical Data

SAB-Del: Subarachnoid Block to Delivery Time.
UI-Del: Uterine Incision to Delivery Time.

When the number of boluses needed to maintain BP was compared, the Group P needed less number of boluses (Table II). Group P 90% patients required single bolus dose and 10% patients required two (2) bolus dose to maintain systolic blood pressure within 20% of basal value.

In Group E 16.67% patients required four (4) bolus dose, 43.33% patients required five (5) bolus dose, 20% six (6) bolus dose, 10% seven (7) bolus dose and 10% eight (8) bolus dose to maintain systolic blood pressure within 20% of basal value.

Number of Bolus Injections	One	Two	Three	Four	Five	Six	Seven	Eight	P value
Group P	27	3	0	0	0	0	0	0	0.000
Group E	0	0	0	5	13	6	3	3	

Table 2. Number of Boluses of Vasopressor Used in Both the Groups

In the Group-P, 23.33% patients required single dose of Atropine to treat bradycardia and 76.67% patients did not require any. In Group E, no patients required any rescue dose of Atropine.

The heart rates at various predefined time points are mentioned in Figure I.

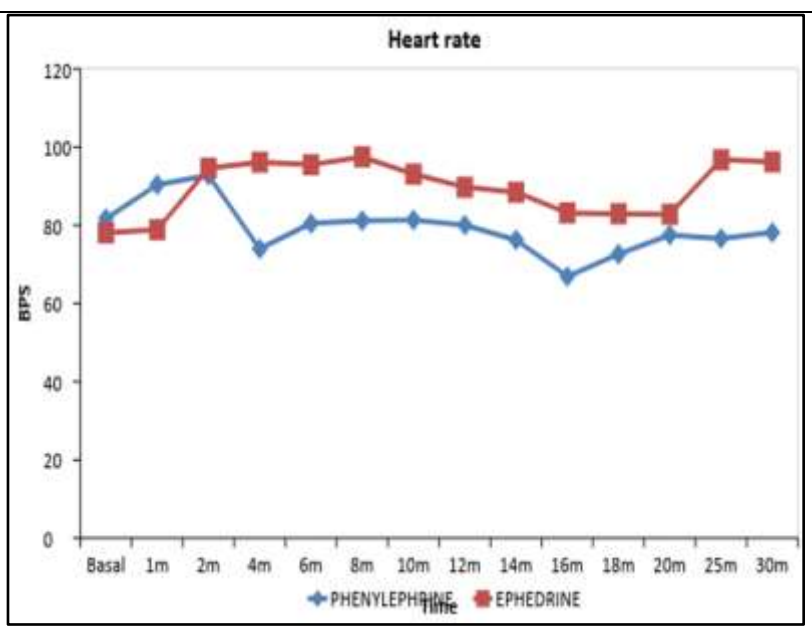

Figure 1. Change in Heart Rate in Predefined Time Points

BPS- Beats Per Second

With the onset of hypotension heart rate increased in both the Groups. In Group P at 2 min heart rate decreased with P value<0.001. At 4 mins heart rate decreased but not significant (P value >0.05). At 6, 8, 10, 12 mins heart rate come to near basal value. At 14 mins it again decreased but not significant (P value >0.05). At 16 mins heart rate significantly decreased (P value<0.001). Thereafter at 18-, 20-, 25- and 30-mins heart rate increased gradually to near basal value. Heart rate decreased after giving study drug and remained decreased till the end of our study (i.e. 30 min)

In Group E, with the onset of hypotension, the increase in heart rate was not significant (P value >0.05). At 2, 4, 6, 8, 10 mins heart rate increased significantly (P value

<0.001). At 12, 14, 16, 18, 20 mins the increase in heart rate above basal value is not significant (P value >0.05). At 25 and 30 mins the increase in heart rate is again significant (P value <0.001).

The change of systolic and diastolic blood pressure can be found in Figure II and III. In Group P, at 2 mins, systolic pressure was significantly below basal value (P value<0.001). At 4 mins, after the study drug had been given, systolic pressure increased to less than 20% of basal value with P value <0.05. At 6-, 8-, 10-, 12- and 14-mins systolic pressure is below normal with P value<0.05. At 16 mins systolic pressure is very significantly decreased (P value <0.001). From 18 mins onwards, systolic pressure increased to near basal level (P>0.05).

In Group E, decreased systolic pressure is very significant (P value <0.001), with more than 20% fall in systolic pressure of basal value at 2 mins. After the study drug given the systolic pressure gradually increased. At 4 mins it was still significantly low. At 6 mins systolic pressure increased significantly to less than 20% of basal value. At 8 and 10 mins though the pressure increased but it was still significantly less from the baseline. Thereafter at 12-, 14- and 16-mins systolic pressure increased near basal level (P>0.05). At 18 and 20 mins again decreased with P value <0.001. At 25 and 30 mins it again increased (P>0.05).

In both the Group the mean value of systolic pressure never touched the baseline.

It can be observed that phenylephrine increased systolic blood pressure at 4 mins while ephedrine increased systolic pressure at 6 mins.

During study period, the diastolic blood pressures were found to be increased significantly in the groups and were statistically significant (P<0.05) only at 4-, 6- and 8- mins. After that till 30 mins it remained insignificant (P>0.05). The magnitude of increase was more in less than 20% of baseline. In group-P it took 4 mins while in group-E it took 6 mins to become less than 20% of baseline. On intergroup comparison, the magnitudes of increase between phenylephrine group at 4 min than ephedrine group which raised blood pressure up to 20% within 6 mins.

Thus, it can be interpreted that both the drugs effectively restored diastolic blood pressure while phenylephrine took 4 mins and ephedrine took 6 mins to maintain within 20% of baseline.

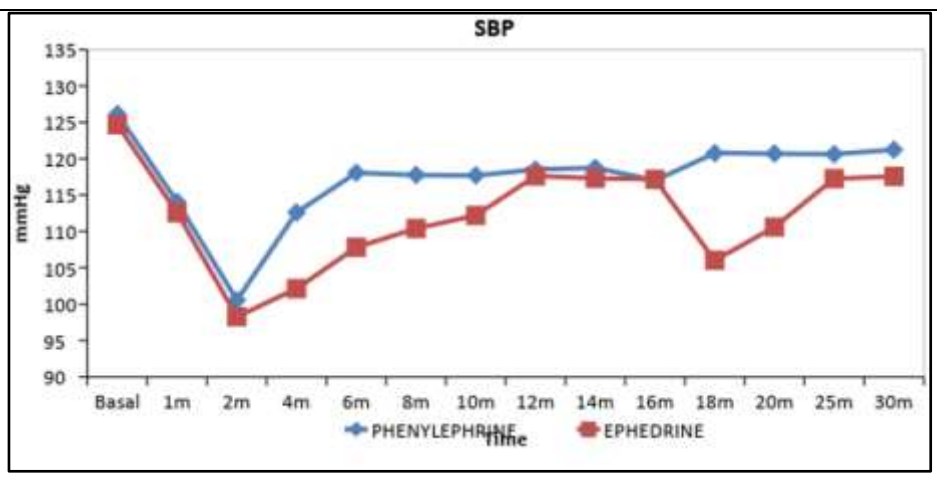

Figure 2. Change in Systolic Blood Pressure in Both the Groups at Various Predefined Time Points

SBP- Systolic Blood Pressure

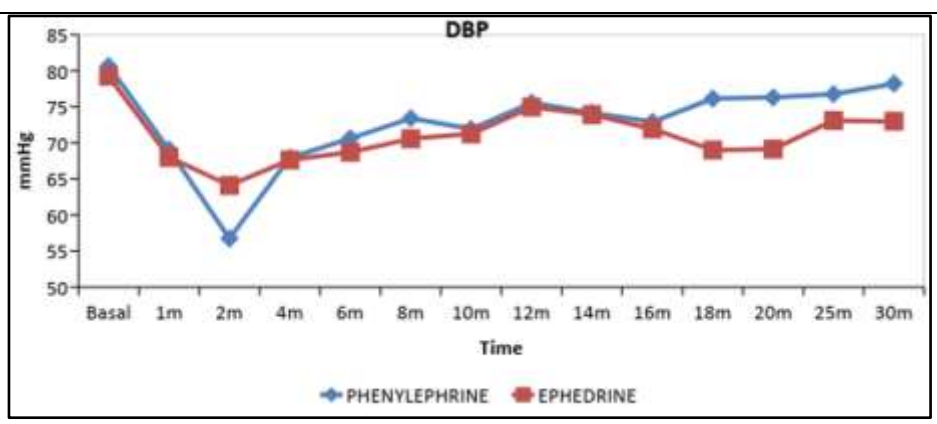

Figure 3. Change in Diastolic Blood Pressure in Both the Groups at Various Predefined Time Points

DBP- Diastolic Blood Pressure

Higher UApH that reached statistical significance was noticed in the patients receiving phenylephrine (Table III)

	Group P		Group E		P value
UApH	Mean	SD	Mean	SD	
	7.377	0.023	7.319	0.021	0.000

Table 3. Umbilical Artery pH in Both the Groups

DISCUSSION

In this prospective randomized study, we observed that less number of interventions to maintain haemodynamics within a predefined range was required if phenylephrine bolus was used. Although the drugs effectively restored systolic pressure, while phenylephrine took around 2 mins, ephedrine took 4 mins to bring systolic blood pressure within 20% of baseline. Although many studies have compared phenylephrine with ephedrine, most of them have used these drugs for prophylaxis.[8,11] Moreover, most of them have used them as an intravenous infusion and used various clinical end points to evaluate the 'effectiveness' of these two agents. Therefore, we conceived to compare the number of boluses needed to maintain the haemodynamics within a predetermined range.

One study from central India observed that in groups of patients receiving phenylephrine, 80% patients required single bolus dose while 15% required two and 5% required three to maintain systolic pressure within 20% of basal value. While in the patients of ephedrine group, 45% required single, 45% two and 10% three bolus doses to maintain the same level of blood pressure.[2] Another study from western India reported that 73.3% patients receiving 100 mcg phenylephrine needed only single bolus, whereas more than 50% in the ephedrine group required two than two boluses.[13] Although the absolute number of patients needing one bolus or multiples of it varied among these studies, it was observed that those receiving phenylephrine needed lesser boluses. Thus, a smaller number of physician interventions was demanded. The study from central India used intrathecal lignocaine, whereas the other study used 2 ml bupivacaine in the intrathecal space.[2,13] None of these studies reports the height of the block obtained. These factors may be responsible for the varying requirement of vasopressors.[14]

Contrary to our and the aforementioned studies, Hall et al and Bhattari et al reported that number of bolus doses of vasopressor required in phenylephrine group was greater than ephedrine group.[7,12] In the study by Hall et al, the boluses were used as a rescue measure if patients developed hypotension in spite of the ongoing intravenous infusion of ephedrine or phenylephrine. Six milligram ephedrine and 20 mcg phenylephrine was used as a rescue bolus. Potency ratio of 81.2 (95%, CI 73.0–89.7) for equivalence between phenylephrine and ephedrine in prevention of hypotension after spinal anaesthesia for Caesarean section has been reported in literature.[8] Thus 20 mcg phenylephrine was not equipotent to 6 mg ephedrine. In the study by Bhattari et al, 6 mg ephedrine was compared against 25 mcg phenylephrine.[12]

In our study, compared to ephedrine, the blood pressure was better maintained with phenylephrine in the first 6 minutes, and similar observations are reported by other authors as well.[2,12,13] The onset of action of phenylephrine is faster and the effect remains for 5-10 minutes depending on the dose and other factors.[15] Whereas, ephedrine not only has delayed onset of action, it also has a longer duration of action of about 60 min.[15] These pharmacological properties may be responsible for the differences of blood pressure and its temporal trend among both the groups.

We observed that the heart rate increased significantly in both the groups at the onset of hypotension. After use of the drugs under evaluation, there was decrease in heart rate in phenylephrine group from baseline whereas increase in heart rate in ephedrine group. The matter of concern was that maternal bradycardia occurred more frequently with phenylephrine than with ephedrine. Similar observations are reported by other authors also.[2,12,13,16] Decrease in heart rate in those receiving phenylephrine is to be expected because an increase in blood pressure with an α-agonist may lead to reactive bradycardia.[2,12,13,15,16] However, this was responsive to atropine treatment without adverse consequences. Maternal bradycardia was not a problem in the ephedrine group because of the β-mimetic effect of ephedrine which would counteract this mechanism.

We also evaluated the UApH. None of the studies that used bolus ephedrine or phenylephrine in the dose that we used, reports any data on UApH. In our study, the newborns in the phenylephrine group had statistically significant increase in umbilical artery pH. SARAVANAN et al found that after titrating the two vasopressors to the same clinical endpoint, a significant but clinically unimportant difference in fetal acidosis was seen between the groups. (8) UApH was significantly (P=0.01) higher at 7.30 (0.06) for phenylephrine compared with 7.25 (0.09) for ephedrine.[8] UApH differences between phenylephrine and ephedrine was 0.050 (95% CI 0.009–0.091). This suggests that hypotension alone was not responsible for the additional acidosis seen in the ephedrine group.[8]

Cooper and colleagues reported increased umbilical arterial minus venous PCO2 (A–V PCO2) difference after ephedrine administration. (4) β-adrenergic stimulation of fetal lamb with isoproterenol has been shown to produce an initial increase in oxygen consumption and an increase in blood glucose and lactate concentrations.[14,15,16] However, it is possible that fetal catecholamine stimulation before delivery might be beneficial. When a β-adrenergic agonist was administered before elective Caesarean section, lower respiratory morbidity, and better lung function and reduced risk of hypoglycaemia in the newborn infant was found. Although, many recent studies have reported conflicting data on acid base status of newborns born to mothers receiving different vasopressor during cesarean section, we suspect that the minor difference in pH may not be of much clinical importance in patients without fetal compromise.

CONCLUSION

In patients posted for elective caesarean section under spinal anaesthesia, fewer boluses are required to maintain maternal blood pressure in a predefined range with 100 mcg phenylephrine IV bolus compared to 6 mg ephedrine. As a secondary objective, we also observed that in patients receiving phenylephrine, there is less maternal heart rate along with statistically significant higher UApH.

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