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Effects of Prophylactic Phenylephrine and Ephedrine Infusion on Maternal Haemodynamics in Elective Caesarean Section under Spinal Anaesthesia: A Comparative Study

Dr Sujata Dalai, Dr Pallab Kumar Mistri, Dr Mohanchandra Mandal,
Prof. Sekhar Ranjan Basu, Prof. Sabyasachi Das,
Assistant Professor, Dept. of Anaesthesiology, Medical College, Kolkata
Associate Professor, Dept. of Obstetrics & Gynaecology, Medical College, Kolkata
Associate Professor, Dept. of Anaesthesiology, NRS Medical College, Kolkata
Professor and Ex-HOD, Dept. of Anaesthesiology, North Bengal Medical College, Darjeeling,
Professor, Dept. of Anaesthesiology, Medical College, Kolkata
Corresponding Author: Dr Pallab Kumar Mistri

Abstract:
Introduction*: The present study was conducted to compare the effects of prophylactic phenylephrine and ephedrine infusion on maternal haemodynamics in elective caesarean section under spinal anaesthesia. It was hypothesized that prophylactic phenylephrine infusion would maintain better maternal haemodynamics than ephedrine infusion.*
Methods*: Seventy six patients were available for randomization into two equal groups to receive either prophylactic infusion phenylephrine 100µg/ml/min (Group P, n=38) or infusion ephedrine 8mg/ml/min (Group E, n=38) after induction of spinal anaesthesia with 10mg hyperbaric bupivacaine with 15µg fentanyl. The infusion was adjusted according to the patient's systolic blood pressure and was administered up to the time of umbilical cord clamping. The incidence of adverse events, if any, was recorded. Apgar scores of every neonate were assessed at 1and 5 minute after delivery.*
Results*: Both the drugs were able to prevent the incidence of hypotension. The systolic blood pressure and bradycardia was higher in phenylephrine group whereas the incidence of tachycardia was the common problem with ephedrine. Also, in phenylephrine group, the maximum upper level of sensory anaesthesia was two segments lower than ephedrine group and there was same neonatal outcome in both the groups.*
Conclusion*: The prophylactic infusion of phenylephrine can be an effective alternative to ephedrine in the prevention of maternal hypotension without imparting any significant neonatal adverse effect. Lesser rostral spread of spinal anaesthetic drug was observed in mother receiving infusion of phenylephrine. However, bradycardia is a common problem with the use of phenylephrine.*
Keywords*: Phenylephrine, Ephedrine, Spinal Anaesthesia.*

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I. Introduction

Now-a-days, spinal anaesthesia is the preferred technique for caesarean section because it avoids the maternal risks of general anaesthesia.[1] But, the incidence of hypotension following spinal anaesthesia in elective caesarean section may be up to 85% without prophylactic management.[2] Maternal hypotension causes reduced uteroplacental blood flow with foetal hypoxia-related stress and maternal symptoms of sudden low cardiac output.[3] To prevent the hypotension with conservative measure a vasopressor drug is necessary to correct hypotension quickly.[4,5]

Since 1927, ephedrine is being used for the prevention and treatment of spinal-induced hypotension. It is often preferred for its potential advantage in maintaining uteroplacental blood flow in spite of its potential demerits such as tachycardia, tachyphylaxis, and foetal acidosis.[3,6,7] King SW and Rosen MA[8] reported that in spite of use of ephedrine either bolus doses alone or bolus dose plus an infusion, the incidence of hypotension remained at 60%. Ngan Kee WD, et al.[9] and Tsen LC, et al.[10] also reported that in spite of prophylactic use of bolus doses of ephedrine, the incidence of hypotension was70-85%.

Recently other studies[6,7,11] have indicated that phenylephrine is better than ephedrine in maintaining maternal arterial pressure. However, Hall PA, et al.[12] found that phenylephrine was less effective in maintaining systolic arterial pressure. In one study[13] the clinical effect of 45 mg ephedrine was found similar to that of 4 mg

phenylephrine, both administered via intramuscular route, while another study[14] showed that boluses of 5-10 mg ephedrine and 40-80 µg phenylephrine were equally effective.
The present study was designed to compare the effects of prophylactic phenylephrine and ephedrine infusion on maternal haemodynamics and neonatal outcome.

II. Materials and Methods

After obtaining Intitute's Ethics Committee's approval, 76 nonlabouring women, aged between 19-35 years, weighing between 50-70 kgs, height 140-165 cm, having singleton pregnancy of gestational age more than 37 weeks, conforming to American Society of Anesthesiology (ASA) physical status I or II, scheduled to have elective caesarean delivery under spinal anaesthesia were included for this study. Mothers having diabetes mellitus, cardiac disease, pregnancy-induced hypertension, cases of foetal anomaly or malpresentation, and patients on chronic medication were excluded from the study. Patient's refusal to accept spinal anaesthesia was also considered an important exclusion criterion.

In the study of Ngan Kee WD, et al. [15] the incidence of hypotension was reduced from 32% in ephedrine group to 4% in phenylephrine group. Considering the α value at 0.05 and power of the study (1-β) at 80%, Sample size of 35 for each group was calculated.[16] Some dropout was expected and hence, a total of 84 patients were initially recruited. Six patients changed their mind to opt out from the study at last moment and hence cannot be included. Thus, 76 patients were available for randomization. The patients were randomly allocated using computer generated random numbers into two groups to receive either prophylactic infusion phenylephrine 100µg/ml/min (Group P, n=38) or infusion ephedrine 8mg/ml/min (Group E, n=38) after the induction of spinal anaesthesia. Allocation concealment was achieved by placing the randomization sequence for each subject in sequentially numbered sealed brown envelopes.

At antenatal clinic, the routine preanaesthetic check up was done to select the patients for this study following the inclusion and exclusion criteria as mentioned earlier. After admission, another preanaesthetic visit was done for every patient on the day before operation to allay anxiety while they were explained about the procedure in their own languages and written informed consents were taken. The patients were premedicated with oral ranitidine 150 mg on the night before and on the morning of surgery. One 18G intravenous (iv) cannula was established and the patient was transferred to the operation theatre in left lateral position. On arrival in the operating room, they were randomly allocated in to two equal groups to receive either prophylactic infusion phenylephrine (Group P, n=38) or infusion ephedrine (Group E, n=38) after induction of spinal anaesthesia. Randomization was done with computer-generated codes contained in sequentially numbered sealed opaque envelopes.

Subsequently, the monitors (ECG, NIBP and SpO_2) were attached. Baseline maternal haemodynamic variables [heart rate (HR), systolic blood pressure (SBP)] were recorded. Intravenous preloading was done with 15 ml/kg of warm lactated Ringer's solution (RL) over 15 minutes, then 5 ml/minute to keep venous patency until clamping of the cord. Proper antiseptic dressing and draping was done. After skin infiltration with 2ml of lignocaine (1%), a 25G Whitacre needle was inserted at the L3-L4 or L4-L5 intervertebral space at left lateral position of the patient. When the clear, free flow of cerebrospinal fluid was obtained, 10mg hyperbaric bupivacaine (5mg/ml) with 15µg fentanyl was injected. The patient was immediately placed in supine left-tilt position (approximately 15 degree) by placing a wedge under the right hip. All patients received oxygen via biprong nasal cannula.

Each patient was allocated to one of the two groups and they were blind about their group allocation. The drug was prepared for the patient according to their group allocation. It was then labelled as study drug and handed over to the blinded anaesthesiologist conducting the anaesthesia. After induction of spinal anaesthesia, the prepared study drug was started to infuse at the rate of 60 ml /hour. Thus, the patients in group P received infusion of drug solution containing phenylephrine (100µg/ml) and patients of group E received infusion of drug solution containing ephedrine (8mg/ml). This dose was selected assuming a potency ratio of 80:1 (phenylephrine 100µg/ml equivalent to ephedrine 8mg/ml) as described by Saravanon S, et al.[17]

Upper level of sensory block was observed 5 minute after spinal injection and every 5 minute thereafter till 30 minute by bilateral pinprick discrimination. Surgeon was allowed to scrub after achieving a sensory block of T5 or higher. After spinal injection, data (SBP, HR) was taken every two minute until the cord clamping.

Subsequently, until cord clamping, the infusion was adjusted with systolic blood pressure measured every 2 minute interval. After which further management was done by the attending anaesthesiologist at his liberty. The infusion was maintained at the rate of 60ml/hour if SBP remained within 90-110% of baseline, halved (30ml/hour) if SBP increased more than 110% of baseline, and stopped if SBP increased more than 120% of baseline, doubled to 120ml/hour if SBP decreased between 80-90% of baseline. When SBP decreased below 80% of baseline, patient was treated with a bolus dose of 100µg of phenylephrine and the episode of hypotension was recorded.

Hypotension was defined when SBP decreased below 80% of baseline value. Hypertension was defined when SBP increased more than 120% of baseline SBP. Bradycardia was defined when heart rate was below 60 beats/min. When HR less than 50 beats/minute, associated with hypotension – was treated with 0.6mg IV bolus atropine, not associated with hypotension – was treated by stopping infusion temporarily. The total dose of the study drug given up to cord clamping, was measured. The incidence of hypotension, hypertension, nausea, vomiting and pruritus were also recorded. One bottle of lactated Ringer's solution containing 10 IU of oxytocin was infused after cord clamping and titrated according to need. The record of the time of spinal drug administration, skin incision, uterine incision, cord clamping was taken.The duration after spinal drug administration to umbilical cord clamping was mentioned as induction-delivery interval, from skin incision to umbilical cord clamping was defined as incision-delivery interval and from uterine incision to umbilical cord clamping was defined as uterine incision-delivery interval. The paediatrician assessed the Apgar scores of every neonate at 1 and 5 minute after delivery.

III. Results and Analysis

Data from 76 patients were available for analysis. The demographic profiles in both groups were comparable. The gestational age, baseline SBP, baseline heart rates also were comparable between two groups. But, there were statistically significant difference with regard to minimum heart rate and maximum heart rate between two groups. The minimum heart rate was 57.68 ± 5.54 beats / minute for group P and 79.87±5.70 beats / minute for group E (table 2) whereas for group P, the maximum heart rate was 85.18 ± 5.66 bpm and 112.63 ± 9.50 bpm for group E (table 2).

Incidence of hypotension and hypertension were comparable between two groups. There was no significant difference in respect to maximum systolic blood pressure but the statistically significant difference between two groups was in respect to minimum systolic blood pressure (table 3).

The incidence of cephalad spread of sensory anaesthesia at different level (thoracic dermatome) in group P and group E were also compared (table-4) and both groups had statistically significant difference(P=0.0000).

Both groups had statistically significant difference for bradycardia(p=0.000) and tachycardia (p=0.000). Incidence of bradycardia in group P was 60.52% but there was no incidence of tachycardia whereas in group E, incidence of tachycardia was 89.47% without incidence of bradycardia. Also, there was no statistically significant difference between two groups in respect to nausea/vomiting. The time intervals from induction-delivery, incision-delivery, and uterine incision-delivery were comparable in both the groups. The neonatal outcome was also comparable between in two groups.

IV. Discussion

Hypotension during spinal anaesthesia is a common problem. To prevent hypotension with conservative measure a vasopressor drug is necessary to correct hypotension quickly.[4,5]

In the present study, both the infusion of prophylactic phenylephrine (100µg/ml) and ephedrine (8mg/ml) were able to prevent the incidence of hypotension in elective caesarean mother under spinal anaesthesia. Both groups have the same incidence of hypotension and hypertension. But, the minimum systolic blood pressure was higher in phenylephrine group than ephedrine group. Phenylephrine is a directly acting α_1-adrenergic agonist, whereas ephedrine is an indirectly acting α-and β-adrenergic agonist. So, phenylephrine is more effective than ephedrine for increased right atrial pressure. Greater right atrial pressure in phenylephrine group might attribute to the higher value of minimum SBP than ephedrine. [18]

The incidence of bradycardia was significantly higher in group P , whereas in group E there was no incidence of bradycardia at all. After discontinuation of phenylephrine infusion the heart rate gradually increased, with no need of atropine. This bradycardia is probably a reflex response to the increased blood pressure due to α- agonistic action of phenylephrine. Stewart A et al.[19], using phenylephrine infusions at the same rate but in different concentrations observed that there was greater reduction of heart rate with higher concentration of this drug used.

Considering the maximum heart rate, there was statistically significant difference between the two groups`(p=0.000). Its mean value was 85.18 ± 5.66 beats per minute in group P and 112.63±9.50 beats per minute in group E. Tachycardia occurring due to β-receptor stimulation is a common problem with ephedrine.

The maximum upper level of sensory anaesthesia with phenylephrine was two segments lower than that with ephedrine. Two previous studies had shown that i.v. phenylephrine decreased the rostral spread of intrathecal local anaesthetics by a median of two dermatomes compared with ephedrine.[18] Phenylephrine being an α-agonist causes vasoconstriction of the epidural veins to a greater degree than ephedrine, thereby reducing epidural vein engorgement. So, phenylephrine may be associated with a decreased epidural space pressure causing lesser rostral spread of spinal anaesthetic drug.

Also, there were same neonatal outcomes as measured by Apgar scores at 1 minute and 5 minute between two groups. A previous study by Lee Anna, et al.[11] also had shown that phenylephrine was associated with similar Apgar scores compared with ephedrine.

In the present study, 10 mg hyperbaric bupivacaine was given intrathecally. Ginosar Y, et al. [20] estimated the ED_{95} of intrathecal hyperbaric bupivacaine dose to be 11mg for successful induction. In another study, Danelli G, et al.[21] determined the ED_{95} of intrathecal hyperbaric bupivacaine to be 0.06mg/cm, based on the patient's height. We selected a dose of 10mg, which was close to these two studies.

There were some limitations of this study. The study population was small and represents one small geographical area. The study could have been designed as a multicentre study involving different ethnic women of larger sample. In that case the result could have been extrapolated for better external validity. The combination of phenylephrine and ephedrine prophylactic infusion could have been used to detect better haemodymic control than prophylactic phenylephrine infusion.

V. Conclusion

The prophylactic infusion of phenylephrine is able to prevent the maternal hypotension like ephedrine without any significant neonatal adverse effect. Lesser rostral spread of spinal anaesthetic drug was observed in mother receiving infusion phenylephrine. But bradycardia is a common problem with this drug.

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Tables:

Table1. Demographic parameters

Parameter	Group P (n = 38)	Group E (n = 38)	p value
Age (years)	24.21± 3.03	23.92± 3.22	0.688(NS)
Weight (kg)	61.45± 2.03	61.05± 3.82	0.577(NS)
Height (cm)	153.87± 3.33	153.92± 3.59	0.947(NS)
BMI(Kg/m2)	26.0±1.59	25.79± 1.87	0.615(NS)
ASA status (I/II) *	21/17	24/14	0.484(NS)
Continuous data are expressed as mean ± SD and are tested using independent Student's *t* test. The data marked * is categorical data which is expressed as number of patients [n (%)] and is analysed using Pearson-Chi square test. A value of p<0.05 are considered as significant. NS, nonsignificant.			

Table 2. Minimum heart rate (bpm), maximum heart rate (bpm) of group P and group E and their statistical analysis.

Parameter	Group P (n = 38)	Group E (n = 38)	p value
Minimum heart rate (bpm)	57.68±5.54	79.87±5.70	0.000*
Maximum heart rate(bpm)	85.18±5.66	112.63±9.50	0.000*
Data are expressed as mean ± SD, Test applied: independent Student's *t* test. *-A value of p<0.05 considered as significant.			

Table 3. Maximum SBP (mm of Hg), minimum SBP (mm of Hg) for group P and group E.

Parameter	Group P (n = 38)	Group E (n = 38)	p value
Maximum SBP(mm of Hg)	145.11±12.57	143.21±8.68	0.447 (NS)
Minimum SBP(mm of Hg)	113.84± 12.16	105.63± 12.13	0.004*
Data are expressed as mean ± SD, Test applied: independent Student's *t* test. *-A value of p<0.05 considered as significant.			

Table-4: The incidence of cephalad spread of sensory anaesthesia at different level (thoracic dermatome) between two groups and their statistical analysis.

Parameters	Group-P (n=38)	Group-E (n=38)	P value
T_1	0	2.63%	0.000*
T_2	0	15.78%	
T_3	2.63%	28.94%	
T_4	15.78%	36.84%	
T_5	36.84%	15.78%	
T_6	36.84%	0	
T_7	7.89%	0	

Test done: Pearson-Chi square test.*p<0.05 considered significant

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