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A CLINICAL COMPARATIVE STUDY OF PROPHYLACTIC INFUSIONS OF PHENYLEPHRINE AND EPHEDRINE ON MATERNAL HEMODYNAMICS AND FETAL ACIDOSIS IN ELECTIVE CAESAREAN SECTION

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ABSTRACT

Keywords:

Prophylactic, Vasopressors, Co-Hydration, Elective Caesarean Section, Hypotension

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Introduction: This randomized double blind study was started with an objective of comparing two commonly used vasopressors – ephedrine and phenylephrine in infusion form with crystalloid co-hydration to reduce spinal anesthesia induced hypotension in elective caesarean section.

Methods: One hundred patients were randomized into two groups to receive either 100 µg/ml phenylephrine (group-P, n=50) or 5mg/ml ephedrine (group-E, n=50). Immediately after spinal injection the study solution was started prophylactically in every patient at the rate of 60ml/hr. A predefined algorithm was used to adjust the infusion rate according to the systolic blood pressure (SBP).

Results: Mean vasopressor required was significantly more in group-P than group-E (p<0.001). Incidence of hypotension were more in group-E than group P. Minimum systolic B.P and time to minimum systolic B.P. was lower in group-E compared to group-P (P value <0.001). Incidence of bradycardia was higher in group P and Incidence of nausea and vomiting was significantly higher in ephedrine group. Umbilical arterial pH and Umbilical Venous pH was lower in group-E and the difference was highly significant (P value <0.001). Apgar score at 5 min was similar in both groups.

Conclusion: Prophylactic phenylephrine infusion provides better maternal hemodynamic control as minimum systolic BP was higher and occurs later in comparison to ephedrine infusion. Incidence of nausea and vomiting was less with phenylephrine compared to ephedrine. Ephedrine causes more acidosis in the fetus. Large doses of phenylephrine were used to maintain a baseline arterial pressure, despite this; there was no adverse effect on the fetus.

INTRODUCTION: Spinal anaesthesia (SA) is nowadays considered the standard anaesthetic technique for elective caesarean section ¹. However, the chance of hypotension is a major limitation of this technique.

The incidence of hypotension is more than 80% without any prophylactic measures ^{2, 3}. This hypotension with or without bradycardia has detrimental effects on both mother and fetus ^{4,5}.

The incidence of hypotension can be lowered by several ways but till date, no single method completely prevents hypotension^{4, 5}. Contemporary articles emphasize on the arterial rather than venous circulation and project the reduced systemic vascular resistance as the primary factor for the genesis of maternal hypotension⁶⁻⁸. Over the last few years, there is a trend to rely more on vasopressors than either crystalloid or colloid alone^{4,6,7}.

Different vasopressors are commonly used at present with varying degrees of success⁶. Despite the use of prophylactic intravenous (i.v.) infusion⁶ or bolus⁷ ephedrine for the last three decades, a good number of failures have also been reported⁹ and a rescue phenylephrine bolus dose appears effective when ephedrine alone fails to correct hypotension³. Prophylactic phenylephrine infusion significantly lowers the incidence of spinal anaesthesia-induced maternal hypotension^{6, 10} despite its limitations like bradycardia, hypertension and reduced cardiac output at higher dose^{3,8}. Advantage of phenylephrine include high efficacy, ease of titration, ability to use liberal doses to maintain maternal blood pressure near normal and prevent nausea and vomiting without causing fetal acidosis. Combination of phenylephrine infusion and rapid crystalloid co-hydration is the first method described that reliably prevents hypotension⁷.

Considering all above aspects, it is planned to carry out a study comparing the effects of phenylephrine infusion and ephedrine infusion with crystalloid co-hydration for preventing hypotension during spinal anaesthesia for cesarean section.

MATERIAL AND METHODS: After obtaining institutional ethics committee's approval, 100 nonlaboring women older than 18 years, American Society of Anaesthesiologists (ASA) physical status I or II, weighing more than 50 kg and less than 90 kg, height 145–165cm, having uncomplicated singleton pregnancy beyond 36 weeks, scheduled to have elective caesarean section under spinal anaesthesia were eligible for this prospective, randomized, double-blind study. Fetal malpresentation, pregnancy-induced hypertension (PIH), hypertension, cardiac disease, renal disease, fetal anomaly, diabetes mellitus and patients on chronic medication were excluded from the study.

Written informed consent was obtained in their own language from every patient during visit one day prior to operation. Hemodynamic variables were noted and patients were advised overnight fasting.

Patients received antacid premedication and standard noninvasive monitoring was applied. We allowed patients to rest undisturbed in the left tilted supine position for several minutes, during which BP was measured every 1–2 min. BP measurements were continued until they became consistent (three successive measurements of SBP that had a difference of no more than 10%). Baseline SBP and HR were calculated as the mean of the three recordings. A 20-gauge intravenous(i.v) catheter was then inserted and vasopressor was given through syringe pump in the same line. No IV preloading was done. IV infusion of lactated Ringer's solution was started at 5 ml/min.

Patients were randomly allocated by block randomization method, where one patient had every chance to get allocated in any group by using computer generated random numbers. The sealed opaque envelope technique was used for concealment. Patients were assigned into two groups to receive phenylephrine 100mcg/ml (group-P) or ephedrine 5 mg/ml (group-E). Either of the vasopressors is supplied to the attending anaesthesiologist in an unlabeled 20 ml syringe, filled up to 12 ml. Two identical 20ml syringes (containing 12ml vasopressor) were prepared containing either phenylephrine 100µg/ml or ephedrine 5mg/ml. One ampoule of phenylephrine (10mg) was dissolved in 100 ml normal saline to make it 100µg/ml. Similarly two ampoules of ephedrine (30mg each) were diluted in 12ml normal saline to make it 5mg/ml.

Spinal anesthesia was induced with patients in the right lateral position. After skin infiltration with lidocaine, a 25-gauge Whitacre needle was inserted at the L2-3 or L3-4 vertebral interspaces, and hyperbaric 0.5% bupivacaine 2.5 ml was injected intrathecally. Patients were then immediately turned supine with left uterine displacement. At intrathecal injection, we started rapid iv fluid infusion (20ml/kg) by fully opening the valve of infusion set with the fluid bag suspended 1.5 m above the operating table and commenced the vasopressor at 60ml/hr.

Blood pressure was measured at 1-min intervals beginning 1 min after spinal injection. Hemodynamic data were downloaded.

Immediately after the completion of intrathecal injection, infusion of study solution was started at the rate of 60ml/hr. Thus, patients of group-P received phenylephrine @100 µg/min, whereas patients of group-E received ephedrine @ 5mg/min. Infusions were administered with a syringe pump that was connected to the i.v line and were continued for a minimum of 2 min, after which the infusion was either stopped or continued according to a predefined protocol based on the SAP measurement each minute.

After each 1-min measurement of SAP, the infusion was stopped if the SAP was more than baseline, and it was continued or restarted if the SAP was less than or equal to baseline. For the purposes of the study, we defined hypotension as a decrease in SAP to <80% of baseline and hypertension as an increase in SAP to >120% of baseline. Each time there was a SAP measurement showing hypotension, patients received a 1-mL i.v bolus of study solution. The dosing regimens for phenylephrine were selected on the basis of recent studies.

Oxygen was not routinely given unless the arterial oxyhemoglobin saturation decreased to <95% when oxygen 5 L/min was given by clear face mask. Any incidences of nausea (reported by patients) or vomiting (observed by investigators) were recorded. We planned to treat nausea or vomiting that was not associated with hypotension with IV metoclopramide 10 mg and to treat bradycardia, defined by an HR <50 bpm that was associated with hypotension, with IV atropine. Five minutes after intrathecal injection, the upper sensory level of anesthesia was measured by assessing loss of pinprick discrimination, and the surgeon was called.

Further checks of the block height were made as required before the start of surgery, but these levels were not recorded as part of the study. The times of skin incision, uterine incision, and delivery were recorded. The infusion and bolus protocol was continued to replace surgical losses and maintain SAP. The total volumes of study solutions given by bolus and by infusions were recorded.

After delivery, oxytocin 10 IU was given by slow IV injection, arterial and venous blood samples were taken from a double-clamped segment of umbilical cord for immediate blood gas analysis with a blood gas analyzer by the attending pediatrician who was unaware of study group. Cases having technical difficulty in performing blood gas analysis were excluded from the study. Apgar scores were assessed 1 and 5 min after delivery by the attending pediatrician.

Presuming the effectiveness of vasopressors over i.v. fluid as 30% and the difference between PE over E as 30% to be clinically relevant, with a power of 80% ($\beta=0.2$) at 0.05 level of significance ($\alpha=0.05$), the sample size was calculated as 44 in each group ($n=44$). We assessed 100 patients for study eligibility keeping the chance of possible dropouts. All the data was tabulated & analyzed with Microsoft Excel 2007. Statistical analysis of data was done using Arithmetic mean & standard deviation. Parametric data among two groups was compared using "unpaired t" test and comparison of non-parametric data was done using chi-square(χ^2) test through Minitab software. "P" value <0.05 was considered statistically significant.

RESULTS: All patients completed the study. The study was done at Swaroop Rani Nehru Hospital, of MLN Medical College, Allahabad during august-2008 to august-2010. Both groups were comparable with regard to demographic profile, pre-operative vital parameters, block height, induction to delivery time and incision to delivery time (**TABLE 1**).

TABLE 1: DEMOGRAPHIC PROFILE, PRE-OP VITAL PARAMETERS

Comparison	GROUP (P)	GROUP (E)	T test (p value)
Age (Mean±SD) (YRS); Range	27.16±5.13(20 – 35)	28.27±4.39(20 –38)	1.17(0.12)
Weight (Mean±SD) (Kg); Range	56.62±4.56(50 – 65)	56.17±2.98(50-60)	0.58(0.28)
Height (MEAN±SD) (cm)	155.5±4.19	156.17±2.98	0.59(0.556)
Baseline Heart Rate Mean ± SD (bpm)	72.23±6	74±5.4	1.54(0.126)
Baseline Systolic BP Mean ± SD (mm Hg)	122.98±6.03	120.23±7.6	1.87(0.064)
Induction to delivery time (Mean ± S.D.) (MIN)	27.45± 2.30	26.5 ± 2.35	1.92(0.058)
Incision to delivery time(Mean ± S.D.)(MIN)	10.98 ± 1.38	10.23 ± 2.57	1.82(0.072)

We found that Prophylactic phenylephrine infusion provides better maternal hemo-dynamic control with less adverse effect on fetus compared to prophylactic ephedrine infusion [TABLE-2] as minimum SBP (Mean \pm S.D.)mm Hg was higher in group- p[106.24 \pm 5.53] compared to group-E[99.12 \pm 7.8] and the difference was statistically significant (P value <0.001) and it occurs (9.29 \pm 1.75)min after spinal in comparison to ephedrine infusion(5.03 \pm 1.32)min. Prevention of hypotension is better with phenylephrine infusion [incidence of hypotension is 8% vs 20% with ephedrine] (TABLE 2).

Phenylephrine causes more bradycardia than ephedrine [8% with group-p vs 2% with group-E and the difference was statistically significant p -value= 0.06] but the incidence of nausea and vomiting was less with phenylephrine [8% compared to 24% with ephedrine (TABLE 2)].

Ephedrine causes more acidosis in the fetus [Umbilical Arterial pH (Mean \pm S.D.) in group-E is (7.20 \pm 0.037) compared to (7.29 \pm 0.008) in group-P (p- value <0.001)]. Large doses of phenylephrine were used to maintain a baseline arterial pressure, despite this; there was no adverse effect on the fetus with phenylephrine

TABLE 2: COMPARISON OF GROUP-P AND GROUP-E

Comparison	Group -P	Group-E	t-test/ χ^2	p-value
Requirement of vasopressor (Mean \pm S.D.)ml	8.52 \pm 1.68	6.7 \pm 1.53	t=35.77	p<0.001
Total iv fluid required (Mean \pm S.D.) (ml)	1177.45 \pm 97.12	1180.39 \pm 80.05	t=0.17	0.86
Incidence of hypotension	8%	20%	$\chi^2=5.025$	0.025
Minimum systolic B.P (Mean \pm S.D.)mm Hg	106.24 \pm 5.53	99.12 \pm 7.8	t=5.18	<0.001
Time to minimum systolic B.P. (Mean \pm S.D.) (Minutes)	9.29 \pm 1.75	5.03 \pm 1.32	t=13.80	<0.001
Incidence of Bradycardia	8%	2%	$\chi^2=4$	0.046
Incidence of nausea and vomiting	8%	24%	$\chi^2=4.76$	0.029
Umbilical Arterial pH (Mean \pm S.D.)	7.29 \pm 0.008	7.20 \pm 0.037	t=15.69	<0.001
Umbilical Venous pH (Mean \pm S.D.)	7.34 \pm 0.007	7.30 \pm 0.022	t=12.8	<0.001
Apgar Score At 5 Minutes (Mean \pm S.D.)	9.90 \pm 0.49	9.78 \pm 0.29	t=1.49	0.14

DISCUSSION: Incidence of hypotension was comparatively lower with phenylephrine infusion (table-2) and minimum recorded B.P occurred later compared to ephedrine infusion (table 2). This reflects pharmacological difference between phenylephrine and ephedrine. Because ephedrine is mainly an indirect acting drug, it has relatively slow onset of action which makes it less effective at preventing the rapid hypotension that typically occurs soon after spinal injection. Ephedrine has a relatively longer duration of action compared to phenylephrine.

Accurate titration of drugs is normally more easily achieved with shorter acting drugs. This study confirmed our clinical impression that starting a prophylactic infusion of phenylephrine immediately after the induction of spinal anesthesia for cesarean delivery would be effective at reducing the incidence, frequency, and severity of hypotension. It is noteworthy that in the phenylephrine group, despite the administration of a large total dose of phenylephrine, the fetal acid-base status and clinical

condition of infants was better (table-2). Appreciating that the mean arterial pressure is a better indicator of tissue perfusion, we have used SBP as a clinically useful endpoint on which our therapy was based and most of the earlier studies have used SBP as primary outcome^{2, 6, 7, 9-15}.

Our findings are consistent with recent published data on management of maternal hypotension during spinal anesthesia⁹⁻¹⁸. Mercier FJ *et al.*, 2007¹⁶ analysed the different preventive and curative strategies for management of hypotension during spinal anaesthesia for cesarean section. Prophylactic phenylephrine, with or without ephedrine according to maternal heart rate, is at least as effective as ephedrine, with less adverse effects. Crystalloid loading at the time of spinal injection ("co-/post-loading") enhances the hemodynamic control provided by vasopressors and concluded that the association of vasopressor (phenylephrine with or without ephedrine) with a rapid crystalloid loading at the time of spinal injection represents the most interesting strategy now-a-days.

We used large total dose of phenylephrine, this may cause concern about potential adverse effects on uteroplacental blood flow. However, the high values for UA and venous pH in our study were indirect evidence that there was no significant adverse effect. It should also be noted that we studied only healthy patients undergoing elective cesarean deliveries. It may not be valid to extrapolate our findings to patients with non-reassuring fetal heart rate patterns or impaired uteroplacental blood flow, to preeclamptic patients, or to patients with prolonged induction to delivery times.

Incidence of Bradycardia: In the present study, the incidence of maternal bradycardia was more in group-P than in group-E (Table 2) and the difference was statistically significant. Different studies have reported varying degrees of bradycardia from no incidence¹⁸ to significant incidence^{4, 11, 17} with phenylephrine than ephedrine. This is to be expected because an increase in blood pressure with an α -agonist may lead to reactive bradycardia. However, this was responsive to atropine treatment without adverse consequences. Lee *et al.*,⁴ suggested that an ephedrine-phenylephrine combination may help prevent maternal bradycardia, as the β -mimetic effect of ephedrine would counteract this mechanism.

Incidence of Nausea and Vomiting: Incidence of nausea and vomiting was significantly higher in group-E (Table 2). Cooper and colleagues¹⁹ suggest that a possible explanation might be an increase in vagal tone following reduction of preload²⁰⁻²³, which is more likely to occur in the presence of beta stimulation²¹⁻²⁴. Cardiac preload decreases with spinal anaesthesia, but phenylephrine, a pure α -agonist, provides better venoconstriction, reducing the decrease in cardiac preload, and diminishing the vagal reflex. This may explain the higher incidence of vomiting after ephedrine.

Fetal Parameters: Umbilical arterial (UA) pH and Umbilical venous (UV) pH was lower in group E. It was consistent with previous studies^{4, 11, 12}. Depression of fetal pH and base excess with ephedrine has been postulated to be related to ephedrine induced stimulation of fetal metabolism¹¹. Ngan Kee WD *et al.*, 2008¹¹ found that UA pH and base excess was lower with ephedrine compared with phenylephrine.

Depression of fetal pH and base excess with ephedrine has been postulated to be related to ephedrine induced stimulation of fetal metabolism. Their results showed that as proportion of ephedrine increased UA pCO_2 was increased and UA oxygen content was decreased without changes in UV values, suggesting an increase in fetal CO_2 excretion and oxygen extraction. Conversely UV pO_2 was decreased as proportion of phenylephrine was increased. This could reflect phenylephrine having a greater vasoconstrictive effect on uteroplacental circulation, since reduction in uteroplacental blood flow has been shown to correlate directly with decrease in fetal pO_2 .

The Apgar score, assessed at 1 minute and 5 minutes, were comparable in all the groups. Current evidence supports that the Apgar score is a better predictor of neonatal outcome than umbilical cord blood gas analysis^{14, 19}.

CONCLUSION: We have found that, when titrated by infusion to maintain arterial pressure during spinal anesthesia for cesarean section, phenylephrine was associated with less fetal acidosis and enabled more accurate control of arterial pressure compared with ephedrine. Phenylephrine infusion has added benefit of lower incidence of nausea, vomiting.

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