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Comparative study between Ephedrine, Norepinephrine and Phenylephrine Infusions in Preventing post Spinal Hypotension during Caesarean Section. A Randomized Controlled Double-Blind Study

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Abstract

Background: Spinal anaesthesia is the popular technique for elective caesarean sections. Though spinal induced hypotension is one of the concerns, vasopressors are more widely used as an effective method for decreasing post spinal hypotension along with fluid loading. However, the ideal vasopressor to prevent spinal hypotension during caesarean section has been a subject of much debate. It should maintain maternal blood pressure and placental perfusion, with minimal adverse effect on foetus and mother.

Aim: This study is aimed to compare the efficacy and safety of prophylactic fixed dose infusion of phenylephrine, norepinephrine and ephedrine in the prevention of post spinal hypotension in elective caesarean section.

Methods: Ninety parturient were randomized into three groups. Group P received phenylephrine infusion at 100 microgram/ml, Group N received norepinephrine infusion at 4 microgram/ml and Group E received ephedrine infusion at 3 miligram/ml. Immediately after spinal injection the study solution was started prophylactically in every patient at the rate of 60ml/hr. Primary outcome measured were the changes in mean arterial blood pressure and heart rate which were recorded throughout the surgery. Secondary outcome measured were neonatal outcome and maternal complications.

Results: Mean Arterial Pressure was higher in the Group E than Group P and Group N and was statically significant. Maternal Tachycardia was maximum in Group E and was statically significant and maternal

bradycardia was more common in Group P but this difference was not statically significant. Incidence of Nausea or vomiting was seen more in Group E. APGAR score at 1 min and 5 min was better with Group N and Group P than with Group E.

Conclusion: Prophylactic fixed dose infusion of phenylephrine and norepinephrine can be used successfully to prevent post spinal hypotension in parturient undergoing elective caesarean section with less maternal side effects and better neonatal outcomes than ephedrine.

Keywords: post spinal hypotension, hyperbaric bupivacaine, nor epinephrine, ephedrine, phenylephrine.

Introduction

For a safe elective caesarean delivery, obstetric anaesthesia guidelines recommend the use of neuraxial anaesthesia, wherever feasible [1]. Hypotension is the most common undesirable side effect associated with spinal anaesthesia in obstetrics anaesthesia [2]. The reported incidences of post spinal hypotension vary between 1.9% and 71% [3]. The most common cause of post spinal hypotension in caesarean delivery is rapid onset of sympatholysis which is due to increased sensitivity of nerve fibers to local anaesthetics during pregnancy [4]. Aortocaval compression due to the pregnant uterus also aggravates the incidence and severity of hypotension, compared to non- obstetric patients [5]. Pregnant women also exhibit an increased level of sympathetic activity compared to parasympathetic activity [4]. Higher sympathetic block also reduces the occurrence of compensatory mechanisms therefore increases the risk of cardio-inhibitory reflexes [5]. Hypotension leads to adverse maternal outcomes such as nausea, vomiting and dizziness [6]. Decrease in systolic blood pressure can compromise uterine blood flow and foetal circulation leading to fetoplacental hypoperfusion and thus cause foetal hypoxia and acidosis. Furthermore, prolonged hypotension may also affect the neonatal outcome [7].

One of the main challenges in obstetric anaesthesia is to find efficient treatment for post spinal hypotension and may include fluid loading during and before spinal (8), lateral position and the use of vasopressor. Vasopressors administration was proven to be essential to manage hypotension in obstetric patients [9].

Ephedrine, phenylephrine and norepinephrine are the three most commonly used vasopressors for managing post spinal hypotension [10]. Ephedrine is a commonly used vasopressor for treatment and prophylaxis against spinal anaesthesia-induced hypotension. Ephedrine has sympathomimetic activity that acts directly as alpha- and beta-adrenergic agonist and indirectly through release of norepinephrine from sympathetic neurons. However, there are concerns about its use as it has potential adverse outcomes that include foetal acidosis, maternal supraventricular tachycardia and tachyphylaxis [11].

Phenylephrine is a pure alpha-adrenergic receptor agonist with no beta-adrenergic receptor activity. It can effectively prevent or treat post spinal hypotension and currently recommended as first line therapy. Despite it could decrease utero-placental perfusion, recent studies have proven that it can improve neonatal outcome by maintaining maternal mean arterial blood pressure and organs perfusion pressure [12].

Recently the vasopressor Norepinephrine has gained popularity in obstetric anaesthesia, it has a weak beta-adrenergic receptor agonistic properties. It has favourable effect on maternal outcome, rendering it a promising alternative to phenylephrine in obstetric anaesthesia [10,13]

This aim of this study is to compare the efficacy and safety of phenylephrine, norepinephrine, and ephedrine fixed dose constant infusions to prevent post spinal hypotension in elective caesarean sections.

Method and material

After taking local ethical committee approval and patient informed consent, this randomized prospective study was conducted in a tertiary care centre in the month of October 2021. Ninety parturient undergoing elective caesarean deliveries with Age group 18-35 years, ASA II, Singleton pregnancy, not in labour and 37 weeks gestation or more were included in this study. Hypertensive patients, patients with cardiac disease, Diabetes Mellitus, multiple pregnancy and emergency LSCS were excluded from this study.

Ninety parturients were randomly divided into 03 groups (30 each). Group P received phenylephrine infusion at 100 microgram/ml, Group N received norepinephrine infusion at 4 microgram/ml and Group E received Ephedrine infusion at 3 miligram/ml. All infusions started just after receiving spinal anaesthesia using syringe infusion pump at the rate of 60ml/hr. Either of the vasopressors is supplied to the attending anaesthesiologist in an unlabeled 20 ml syringe, filled up to 12 ml. Three identical 20ml syringes (containing 12ml vasopressor) were prepared containing either phenylephrine 100µg/ml or ephedrine 5mg/ml

Drug preparation

Group P- One ampoule of phenylephrine (10mg) was dissolved in 100 ml normal saline to make it 100µg/ml.

Group N- half ampoule of nor adrenaline (2000 µg) was dissolved in 500ml normal saline to make it 4µg/ml

Group E- Two ampoules of ephedrine (30mg each) were diluted in 20ml normal saline to make it 3mg/ml.

On arrival to operating room, patients were monitored using electrocardiogram, non-invasive arterial blood pressure, and pulse rate and SpO2. Three readings of non-invasive blood pressure (at 1-min interval) were recorded. The average of the three readings of mean arterial blood pressure (MAP) was used as baseline. Intravenous cannula of 16 gauge was inserted in one arm and was preloaded with ringer lactate at 10ml/kg. Patients were given antiemetic prophylaxis metoclopramide (10 mg IV). Under strict aseptic precaution spinal anaesthesia was performed in the sitting position. The spinal anaesthesia was given at L2-3 or L3-4 interspace. Intrathecal injection of bupivacaine heavy 0.5% in a volume of 2.0 ml was given intrathecally. Then, parturient was placed in supine position with a left lateral tilt of 15-20 degrees and pillow supporting the head and shoulders. Supplemental oxygen (4 L/min) by a clear face mask was started.

Immediately after spinal anaesthesia, Heart rate and mean arterial blood pressure of parturient were recorded immediately from the time of receiving spinal anaesthesia, then every 5 min until skin closure. A vasopressor infusion pump started according to type of the group. The infusion rate was constant, Each time MAP decreased to more than 20% of baseline, patients received a 1-mL i.v bolus of study solution. If bradycardia (heart rate <50 beats/min) developed, intravenous atropine (0.01 mg/kg) was administered. After delivery, an intravenous infusion of oxytocin (20 IU) was slowly administered. Apgar score of foetus was assessed at 1 and 5 min after delivery was recorded. Total duration of surgery, maternal nausea and vomiting and other side effects was recorded. Parametric data was expressed as mean±SD, the comparison of quantitative data was done

using STUDENT T TEST with p value <0.05 was taken to be statistically significant.

Results

A total of Ninety partiuent were randomly divided into 3 groups (30 each). There was no significant difference in the studied groups according to demographic data. In addition, variables as duration of surgery and number of interventions (number of boluses of studied drugs), there was no significant difference in studied drugs according to these variables. Although more bolus doses were given in group E (5 boluses) than in other groups P and N (2 boluses each) (Table 1).

There was no statistically significant difference between studied groups in baseline values of maternal heart rate. Maternal heart rate increased significantly in Group E in comparison with Group P and Group N. The maternal heart rate was significantly decreased in Group P than in Group N (Table 2)

There was no significant difference among the three groups in baseline mean BP. However, maternal mean blood pressure significantly high in Group E in comparison with Group P and Group N. Mean blood pressure was significantly higher in Group P than in Group N (Table 3)

Apgar score at 1st and 5th minutes was lowest in Group E and highest in Group N. As regards maternal complications nausea and vomiting was highest in Group E and minimum in Group N, Maternal tachycardia and hypertension was maximum in Group E and was minimum in Group P. Although, five patients experienced maternal bradycardia in Group P, while no case was observed in Group N and in Group E (Table 4).

Table 1: Comparison between studied groups as regards to demographic data, duration of surgery and number of rescue bolus doses.

	GROUP P (n=30)	GROUP N (n=30)	GROUP E (n=30)	Student t test P value		
	Mean ±SD	Mean ±SD	Mean ±SD	PN	NE	PE
Age (yr)	24.64 ±3.0	25.5±3.7	26.04±5.2	0.326	0.644	0.206
Weight	76.16±6.3	76.4±6.2	79.5±8.0	0.824	0.122	0.077
Duration of surgery	42.4±3.9	39.8±7.0	40.2±5.2	0.080	0.802	0.068
No of boulses doses	2	2	5			

Table 2: Comparison between studied groups as regards with maternal heart rate.

	GROUP P (n=30)	GROUP N (n=30)	GROUP E (n=30)	STUDENT T TEST P VALUE		
HEART RATE	Mean ±SD	Mean ±SD	Mean ±SD	PN	NE	PE
BEFORE ANAESTHESIA	89.3±4.96	92.01±8.6	92.1±8.4	0.140	0.967	0.121
AFTER 5 MIN	89.7±7.2	90.3±9.2	94.6±9.2	0.779	0.075	0.025

10 MIN	79.48±6.5	86.44±9.5	94.9±7.3	0.001	0.003	0.001
15 MIN	78.32±5.4	83.42±9.8	89.3±10.1	0.015	0.023	0.001
20 MIN	76.47±4.2	82.82±7.5	88.9±9.2	0.002	0.006	0.001
25 MIN	74.0±8.4	79.72±6.4	88.8±12	0.004	0.006	0.001
30 MIN	74.6±7	77.7±9.1	86.9±12.8	0.018	0.002	0.001
35 MIN	70.6±5	78.7±5.4	87.2±11.9	0.001	0.001	0.001
40 MIN	70.9±5.6	79.3±2.2	85.9±9.2	0.001	0.003	0.001
45 MIN	71.0±3.4	78.9±5.2	87.2±2.1	0.001	0.001	0.001

Table 3: Comparison between studied groups as regards to maternal mean blood pressure.

	GROUP P (n=30)	GROUP N (n=30)	GROUP E (n=30)	STUDENT T TEST P VALUE		
MAP	Mean ±SD	Mean ±SD	Mean ±SD	PN	NE	PE
BEFORE NAESTHESIA	79.7±5.8	76.48±6.4	78.1±6.14	0.051	0.321	0.303
AFTER 5 MIN	72.4±6.2	67.6±7.0	68.9±5.2	0.006	0.417	0.021
10 MIN	71.2±5.7	66.7±6.1	69.9±6.2	0.004	0.048	0.401
15 MIN	71.94±3.2	69.4±3.2	74.92±7.2	0.003	0.003	0.042
20 MIN	72.9±5.1	79.94±3.8	75.9±4.4	0.001	0.003	0.017
25 MIN	73.4±4.56	75.84±3.5	77.84±3.5	0.023	0.030	0.001
30 MIN	76.1±3.1	73.2±4.6	80.1±3.5	0.005	0.001	0.001
35 MIN	75.8±5.2	71.8±4.2	81.96±4.2	0.001	0.001	0.001
40 MIN	76.9±4.6	73.9±4.3	82.0±4.6	0.011	0.001	0.001
45 MIN	78.6±3.4	75.2±5.5	82.8±4.3	0.005	0.001	0.001

Table 4: Comparison between studied groups as regards to Neonatal outcome and maternal complications.

	GROUP P (n=30)	GROUP N (n=30)	GROUP E (n=30)
APGAR SCORE			
1 MIN	9 (7-10)	9 (8-10)	8 (6-10)
5 MIN	9 (8-10)	9 (8-10)	8 (7-10)
NAUSEA	2	0	2
VOMITING	2	0	3
HYPERTENSION	0	2	2
TACHYCARDIA	0	1	4
BRADYCARDIA	5	0	0

Discussion

The aim of this study was to compare the efficacy and safety of prophylactic fixed dose infusion of phenylephrine, norepinephrine and ephedrine in the prevention of post spinal hypotension in elective caesarean section. Ninety parturient were enrolled in this study. The results of this study showed that mean arterial blood pressure was better maintained with a prophylactic fixed dose infusion of either phenylephrine or norepinephrine compared with those who received prophylactic fixed dose ephedrine infusion. Tachycardia was associated more with Group E and bradycardia with Group P. Fetomaternal outcome was comparatively better in Group P and Group N then group E. The reduction of systematic vascular resistance (SVR) is the main mechanism involved in post spinal hypotension which is secondary to vasodilatation [14,15].

In our study we found that both phenylephrine and norepinephrine are better choices than ephedrine in controlling maternal MAP of post spinal hypotension during caesarean delivery. Ephedrine group needed more boluses in between top up along with continuous fixed dose infusion to control hypotension than in phenylephrine and norepinephrine groups. These results were comparable to other studies where ephedrine could not prevent hypotension in low doses by infusion, so it failed to be used for prophylaxis against hypotension. In addition, in other groups, those who were treated with noradrenaline and phenylephrine needed fewer rescue boluses as compared to ephedrine [16][17].

In our study the maternal heart rate was highest with Group E and lowest in Group P. Our results were similar to a study conducted by Xian Wang [18] which were consistent with their respectable pharmacological properties. Ephedrine has sympathomimetic activity that acts directly as alpha- and beta-adrenergic agonist and indirectly through release of norepinephrine from sympathetic neurons. Phenylephrine is a pure alpha-adrenergic receptor agonist with no beta-adrenergic receptor activity. Norepinephrine has alpha-adrenergic and weak beta adrenergic receptor agonist property, which has a favourable effect in maternal heart rate and cardiac output.

In our study a minimum APGAR score at 1 min was 06 and this was associated with Group E. Ngan Kee et al. [19] explained that depressed foetal acid– base status due to ephedrine crossing the placenta and associated with greater foetal concentrations of lactate, glucose, and catecholamine because of the metabolic processes in the foetus caused by activation of foetal β-adrenergic receptors.

Regarding of maternal complications, the most important observation was modest bradycardia related to phenylephrine infusion, which was transient and occurred only in five cases (HR <50 per min) in comparison with no cases in Group N and Group E and that was managed by 0.01 mg/kg I.V. atropine, while maximum tachycardia was associated with Group E (04/30). Hypertension was observed equally more in both Group E and Group N (02/30). These findings were in accordance with other previous studies [2,9,13,17].

Nausea and vomiting are common complications in obstetric anaesthesia. There was no case observed with nausea or vomiting in Group N. Vomiting was observed more with Group E (03/30) than Group P (02/30) while nausea was observed equally in Group E (02/30) and Group P (02/30), which was responded

rapidly to injection metoclopramide 10 mg IV. The possible cause of nausea and vomiting may be the increase of vagal tone following the reduction of preload as documented by Cooper et al. [20]. None of the patients observed severe complications or intensive care admission.

Conclusion

This study results showed that fixed dose continuous infusion of both norepinephrine and phenylephrine are superior than ephedrine in preventing post spinal hypotension during elective caesarean section. Norepinephrine is found more effective than phenylephrine in terms of controlling maternal heart rate and nausea or vomiting. Therefore, noradrenaline infusion can be a alternative to phenylephrine infusion in controlling post spinal hypotension in caesarean delivery.

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