ORIGINAL ARTICLE

COMPARISON OF SINGLE BOLUS NOREPINEPHRINE WITH PHENYLEPINEPHRINE FOR PREVENTION OF HYPOTENSION DURING CAESAREAN SECTION UNDER SPINAL ANAESTHESIA

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Background: Hypotension remains the main concern following spinal anaesthesia in patients planned for caesarean section. A number of pharmacological agents has been used prophylactically to prevent hypotension in past. Norepinephrine and phenylepinephrine are the two most commonly used agents. Aim of this study was to evaluate the effectiveness of these two agents used as single bolus for prevention of hypotension during caesarean section under spinal anaesthesia. **Methods:** This Quasi-experimental study was conducted in Department of anaesthesia, Punjab Rangers Teaching Hospital Lahore. A total of 180 patients (90 in each group) fulfilling the inclusion criteria were included in this study. Patients were divided into two groups by using lottery method. Group-A (PE group) received phenylepinephrine bolus while Group-B (NE group) received norepinephrine bolus under spinal anaesthesia. Blood pressure (primary outcome) and heart rate (secondary outcome) was recorded for 20 minutes at five-minute interval. Incidence of hypotension and bradycardia was recorded in both groups. Presence of hypotension alone or with bradycardia in both groups was treated with intravenous crystalloid bolus @ 10ml per kg body weight. Persistent hypotension with bradycardia despite crystalloid bolus treated with a rescue bolus of intravenous atropine 0.6 mg was considered the endpoint. **Results:** 33.3% (n=30) in PE Group while 18.9% (n=17) in NE Group developed hypotension with p value of 0.04. Similarly, 20% (n=18) in PE Group as compared to 4.4% (n=4) in NE Group had bradycardia showing statistically significant difference between the two groups with p value of 0.02. Regarding need of rescue atropine bolus, n=5 (5.5%) in PE Group while n=1 (1.1%) in NE Group required it with calculated *p*-value of 0.09. **Conclusion:** We concluded that prophylactic bolus of norepinephrine was more effective than phenylepinephrine in prevention of post spinal hypotension and bradycardia during caesarean section with better maintenance of systolic blood pressure and heart rate.

Keywords: Hypotension; Norepinephrine; Phenylepinephrine; Spinal anaesthesia.

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INTRODUCTION

Neuraxial anaesthesia techniques as spinal and epidural anaesthesia have evolved as the preferred techniques for caesarean section not only because of their predictable and quick onset of action but also due to prevention of untoward effects of general anaesthesia on mother and fetus.[1] Neuraxial techniques also prevent airway manipulation and its associated complications in general anaesthesia.[2] However, the main concern of spinal anaesthesia during caesarean section is the hypotension resulting from blockage of sympathetic outflow.[3] Post spinal anaesthesia hypotension incidence is estimated to be as high as 60–80% demanding its active prevention by pharmacological measures using different vasopressor agents.[4]

A number of pharmacological agents have been used in past to prevent spinal associated hypotension during caesarean section but none of them has been found to be fully effective and without untoward side effects or concerns over mother or fetus.[5] Initially ephedrine was used for this purpose but it was found to cause maternal tachycardia and a decrease in foetal pH during foetal umbilical blood sample analysis in early neonatal period.[6] Later, Phenylephrine replaced ephedrine as vasopressor of choice as it has less effect on foetal pH but its use was reported to be accompanied by a dose dependent receptor mediated decrease in maternal heart rate and cardiac output leading to compromised placental blood flow.[7] Recently, norepinephrine has emerged as new agent as it has minimal effects of maternal blood pressure and heart rate owing to its dual α and β receptor agonist properties.[8]

Vasopressor agents can be used as single bolus, multiple rescue boluses or as continuous infusion during surgery to prevent post spinal hypotension during caesarean section.[9] None of these techniques is reported to be superior to other for the said purpose. However, continuous infusion and repeated rescue boluses need

dose titration according to patient response and increase the clinician workload which can affect the monitoring and management during surgery.

The objective of this study was to compare the effectiveness of frequently used vasopressor phenylepinephrine with new agent norepinephrine given as single bolus for hypotension prophylaxis during caesarean section under spinal anaesthesia.

MATERIAL AND METHODS

This study was conducted at anaesthesia Department, Punjab Rangers Teaching Hospital Lahore, from March 2024 to August 2024 after obtaining approval from hospital ethical committee (ethical committee/ IRB Ref no 26/2004). The sample size was calculated using the WHO sample size with anticipated population proportion 1 (P_1) 0.35, anticipated population proportion 2 (P_2) 0.25, absolute precision required (d) 0.08 and 90% confidence level[10]. One hundred eighty patients were divided into two groups of 90 each after obtaining informed written consent by using the simple random probability sampling, with group PE received bolus of phenylepinephrine while group NE received norepinephrine bolus keeping the primary researcher blind to both groups.

The study included pregnant females classified as grade I or II according to the American Society of Anesthesiologists (ASA) criteria, with a singleton term pregnancy scheduled for elective caesarean section. Exclusion criteria comprised pregnant females diagnosed with gestational diabetes mellitus, preeclampsia, or eclampsia; those with underlying cardiac conditions; cases involving twin pregnancies; individuals presenting with placenta previa or placenta accreta; and those experiencing fetal distress.

All the patients were kept nil per oral overnight and were given metoclopramide 10 mg and ondansetron 8mg both intravenously as premedication. On arrival in operating room, electrocardiogram leads, non-invasive blood pressure (BP) monitoring cuff, and SpO2 monitors were attached. Baseline heart rate (HR) and BP were noted by taking an average of three values recorded at an interval of 3 minutes with the patient in supine position. An 18G IV cannula was placed and loading was achieved using 500 mL of lactated Ringer lactate solution. Another wide-bore IV cannula was placed in the contralateral arm for emergency resuscitation use. Spinal block was given with 15 mg hyperbaric bupivacaine in the L3-L4 intervertebral space using a 25 G spinal needle with the patient in sitting position. After the block, patients were made supine with left lateral tilt.

The effectiveness of spinal block was assessed with loss of painful pinprick sensation on both sides at the level of T4-T5 dermatome. Once effective spinal block is achieved, group A was given phenylepinephrine intravenous bolus @ 0.4ug per kg body weight and group B received norepinephrine intravenous bolus @ 0.06ug per kg body weight (based on calculated ED50 values of both drugs).[11] Both agents were diluted in 10ml distilled water and given as slow bolus over 5 minutes. Followed by intravenous vasopressor bolus, gynaecologist was asked to proceed with surgery. BP and HR values were recorded at intervals of every five minutes till 20 minutes following spinal anaesthesia. Hypotension was defined as a decrease in systolic blood pressure (SBP) of ≤20% of baseline values or less than 90 mmHg. Heart rate (HR) lower than 60 beats per minute was defined as bradycardia. Patients having hypotension alone or with bradycardia were treated with intravenous crystalloid bolus @ 10 ml per kg body weight. Persistent hypotension with bradycardia despite crystalloid bolus was treated with a rescue bolus of intravenous atropine 0.6 mg. Immediately after delivery, 10 IU of oxytocin were administered as a slow bolus over 10 to 15 seconds followed by 20 IU started as a slow infusion in intravenous drip. Paracetamol 1 g intravenous was given before shifting the patient to postoperative recovery area for postoperative pain.

Primary outcome of our study was to compare the incidence of maternal hypotension in patients receiving bolus of phenylepinephrine with norepinephrine in spinal anaesthesia for caesarean section while secondary outcome was to compare the incidence of maternal bradycardia in both the groups.

SPSS version 22 was used for data analysis. Mean and standard deviation was calculated for quantitative data as age, gestational age, systolic blood pressure and heart rate. For qualitative data as incidence of hypotension and bradycardia, frequency and percentage were calculated. Independent sample t test was used for comparison in both groups and *p*-value of <0.05 was considered as significant.

RESULTS

180 patients were divided into two groups of 80 patients each. Group A received phenyepinephrine bolus (PE Group) while group B received norepinephrine bolus (NE Group). Mean±Sd for age in group PE was 28.89±3.98 years while it was 27.97±3.62 years in group NE. Similarly, Mean±Sd for gestational age in group PE was 38.05±1.29 weeks while it was 37.72±1.48 years in group NE. Calculated *p*-value for age and gestation age was 0.11 and 0.12 respectively showing no statistically significant difference between the two groups.

Parameters of preoperative and serially measured mean SBP and HR at 5, 10, 15 and 20 minutes in both groups with calculated *p*-values are shown in table-1.

Serial change in mean SBP and HR are plotted at five intervals as shown in Figure 1 and 2 respectively. Mean drop in SBP in PE group from start till 20-minute post bolus was 16.4 while it was found to be 13.9 in NE

group. For serial change in HR, mean drop in HR is 14 in PE group as compared to 10.2 in NE group. Regarding incidence of hypotension in both groups, n=30 in PE Group while n=17 in NE Group developed hypotension with *p*-value of 0.04. Similarly, n=18 in PE Group as compared to n=4 in NE Group had bradycardia showing significant difference between two groups with *p*-value of 0.02, as shown in chart 3. Regarding need of rescue atropine bolus, n=5 (5.5%) in PE Group while n=1 (1.1%) in NE Group required it with calculated *p*-value of 0.09 showing no statistically significant difference between the two groups

Table-1: Operative parameters in both groups

Parameter	PE Group	NE Group	*p*-value
Pre-delivery SBP	119.51±5.77	118.12±4.76	0.08
SBP 5 minutes post bolus	116.32±5.34	115.53±4.40	0.28
SBP 10 minutes post bolus	112.23±6.38	112.58±4.22	0.66
SBP 15 minutes post bolus	107.03±9.38	108.68±6.01	0.16
SBP 20 minutes post bolus	102.71±10.75	104.15±9.34	0.33
Pre-delivery HR	83.01±7.66	83.13±5.74	0.89
HR 5 minutes post bolus	79.31±7.91	81.79±6.62	0.02
HR 10 minutes post bolus	75.72±7.87	78.60±7.05	0.01
HR 15 minutes post bolus	71.84±8.26	74.62±7.07	0.02
HR 10 minutes post bolus	69.02±6.98	71.15±7.10	0.04

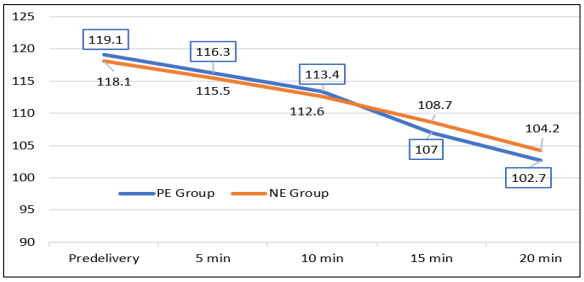

Figure-1: Intraoperative serial change in mean SBP.

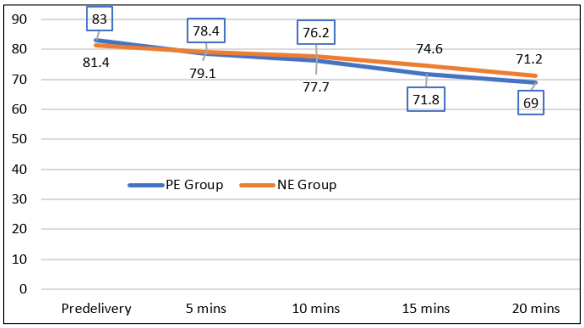

Figure-2: Intraoperative serial change in mean HR.

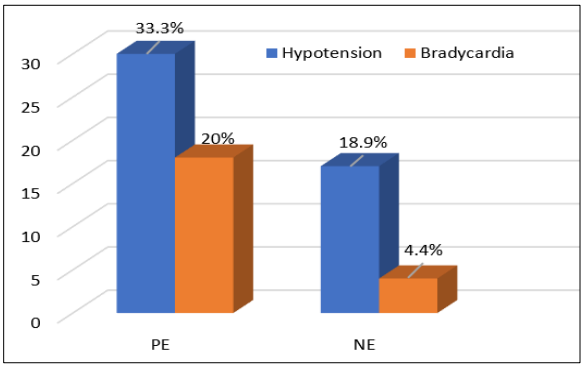

Figure-3: Incidence of hypotension and bradycardia in both groups.

DISCUSSION

This study evaluated the effectiveness of phenylepinepphrine and norepinephrine in preventing spinal anaesthesia associated hypotension and bradycardia in elective caesarean section with results showing norepinephrine superiority having statistically significant difference between the two groups. Ephedrine used to be considered the first line vasopressor for hypotension prophylaxis during caesarean section under spinal anaesthesia but it has slow onset of action along with prolonged duration of action making accurate and valid measurement of blood pressure difficult with its use. This drug also causes more disruption in foetal acid base profile. Later, phenylephrine, a pure alpha agonist replaced ephedrine as it has less pronounced effects of foetal acid base balance due to its limited placental transfer and can be used as either bolus or continuous infusion but its main drawback is reflex mediated maternal bradycardia which can cause decrease in maternal cardiac output. This concern limits its use in patients with pre-existing cardiac comorbidities and in cases where foetal distress is already present. Most recently, norepinephrine has emerged as new vasopressor of choice as it has positive effect on maternal heart rate due to its weak beta agonist adrenergic effect.

In our study, there was no difference in age and gestation age in both groups which was in accordance to a study conducted by Pauline A and colleague.[12] Similarly, predelivery SBP and HR were comparable in both groups in our study showing no gross difference in these parameters before the intervention. Serial measurement of SBP in both groups did not reveal any statistically significant difference at any measured interval but mean SBP gradually improved in NE group following 10 minutes of bolus administration. Similarly, plotting of serially

measured mean HR in both groups revealed improved mean HR near 10 minutes post bolus in NE group compared to PE group earlier than change in mean SBP in both groups. These findings can be explained by the weak beta agonist action of norepinephrine producing a positive chronotropic effect compared to the dose related reflex bradycardia caused by norepinephrine.[13]

Incidence of hypotension was found to be 33.3% in PE group compared to 18.9% in NE group in our study with statistically significant difference between the two study groups. This incidence was comparable to the findings reported by Ravichandrane B and colleagues.[10] Their study also supports finding of statistically non-significant pre delivery HR as well as number of rescue boluses required in both groups in accordance to our study. Although there was no statistically significant difference with regard to serial mean SBP in our study but the incidence of hypotension was much lower in NE group dictating a better hemodynamic profile offered by norepinephrine due to compensated rise in HR preventing drop in mean SBP and in turn avoiding hypotension. Similar findings were reported by Sharkey *et al* in their study by using intravenous intermittent boluses of phenylephrine and norepinephrine showing superior hemodynamic and safety profile of norepinephrine in prevention of spinal associated hypotension during caesarean section[14]. Similarly, Ngan k *et al*[15] showed that norepinephrine was more effective in maintaining blood pressure with better mean heart rate once compared with phenylephrine by using computer-controlled infusion system. Our study is unique in the sense that we opted to use single bolus of both drugs given at calculated dose of ED50. Literature review revealed that norepinephrine is more superior in preventing hypotension in elective caesarean section once given at ED90 but at the cost of increased incidence of nausea in postoperative period along with reported reactionary hypertension in some cases.[16] As we have used ED50 in our study, we did not report any case of reactive hypertension or any other notable adverse event. By using ED50, we also tried to neutralize specific dose related bradycardia effects associated with phenylepinephrine. Previous studies have used continuous or fixed infusions protocols of different vasopressors to delineate their effect on post spinal hypotension and bradycardia in caesarean delivery but infusions are difficult to titrate as well as their sudden abruption can actually potentiate the hypotensive episode owing to persistence of autonomic blockade from spinal anaesthesia even after delivery. Similarly, oxytocin administration can further decrease maternal blood flow due to peripheral vasodilation causing transient hypotensive episode which can interfere with results of vasopressor infusion producing high false positive hypotensive incidence.[12] Therefore, single bolus vasopressor shot was used in our study to negate such confounding factors.

Regarding incidence of bradycardia in our study, statistically significant difference was found between two groups. This finding is in accordance to a study conducted by Liu P and colleagues.[17] In a study conducted by Theodoraki K[13], the reported incidence of bradycardia was 4.8% in NE group which was in accordance to our study. However, they reported a much higher bradycardia incidence of 31.7% in PE group which could be explained by low sample size of 41 and use of fixed continuous infusion of 50ug per minute in phenylepinephrine group, a dose greater than calculated ED50 used in our study. Another study conducted by GUO L and colleagues showed bradycardia incidence of 24.6% in PE group compared to 7.2% in NE group with calculated p value of 0.005 by using dose fixed vasopressor infusion in both groups. Our study had produced similar results with the use of single bolus vasopressor showing that single shot vasopressor option is equally effective but more manageable as compared to previously recommended infusion protocol.[18] Another potential benefit of norepinephrine is its cost effectiveness as compared to phenylepinephrine which is beneficial to resource limited set ups like ours.[12] Although foetal outcomes were not considered in our study, a previous study conducted by Wang X et al had shown superior foetal parameters soon after delivery with enhanced safety profile of norepinephrine for foetus in comparison to other vasopressors used to treat post spinal hypotension in caesarean delivery.[19]

The only literature reported concern associated with use of norepinephrine in peripheral line is danger of skin necrosis caused by vasoconstriction. This can particularly happen in cases where tissue extravasation occurred during administration. However, studies have proved that this concern is only of theoretical importance and norepinephrine can be safely administered in peripheral vein via either infusion or bolus form.[14] In our study, we did not report any such adverse effect as diluted bolus was given over 5 minutes with special care to prevent extravasation.

CONCLUSION

We concluded that prophylactic bolus of norepinephrine was more effective than phenylepinephrine in prevention of post spinal hypotension and bradycardia during caesarean section with better maintenance of systolic blood pressure and heart rate. Prophylactic single bolus vasopressor had produced similar results compared to use of vasopressor infusion. Norepinephrine may be used as

first line vasopressor for prevention of post spinal hypotension in caesarean section.

Conflict of Interest: None.
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AUTHORS' CONTRIBUTION

MP: Conceptualization of study design, data collection, write-up. RMH: Literature search, proof reading. MMS: Data analysis, data interpretation.

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