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RESEARCH ARTICLE

Comparative study of norepinephrine and phenylephrine infusion for prophylaxis against post-spinal hypotension in patients undergoing elective cesarean section

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ABSTRACT

Background: Maternal hypotension is a physiological response during cesarean section (CS) with spinal anesthesia (SA) and can cause adverse maternal and fetal outcomes. **Aim:** The present study aimed at comparing the efficacy and safety of norepinephrine and phenylephrine infusion in a CS under SA. **Methods:** In a randomized clinical trial, 164 ASA I and II parturients undergoing CS under SA were randomized to have a prophylactic infusion of norepinephrine 0.05 µg/kg/min (group N) or phenylephrine 0.75µg/kg/min (group P). The primary outcome was the incidence of post-spinal hypotension. Incidence of severe post-spinal hypotension, reactive hypertension, and bradycardia, total vasopressor rescue bolus doses required, number of physician interventions, nausea and vomiting, and Apgar score at 1 and 5 mins were secondary outcomes. **Results:** The incidence of post-spinal hypotension in group P (24 %) and group N (29.26 %); severe post-spinal hypotension in group P (3.6 %) and group N (2.4%) respectively and were comparable (p-value >0.05). No of bolus dose of vasopressor required between the two groups, and the incidence of bradycardia and reactive hypertension were comparable. Nausea and vomiting were very low in both groups and comparable. The number of physician interventions needed was significantly higher in group P (39.02%) compared to group N (28.04%) (p-value < 0.05). **Conclusion:** Norepinephrine is associated with a lower number of physician interventions as compared to phenylephrine; otherwise, hemodynamics is comparable when used to prevent hypotension.

Keywords: Norepenephrine, phenylephrine, caesarean section, spinal anaesthesia.

Regional central-neuraxial anesthesia, primarily spinal anesthesia (SA) is the anesthetic technique of choice for elective cesarean section (CS).[1] Maternal hypotension is a physiological response during CS with SA and it is thought to be a major factor in the development of adverse maternal outcomes like nausea, vomiting, dizziness, and even cardiovascular collapse. Additionally, fetal acidosis, hypoxia, and even postnatal neurological injury are concerns prompted by compromised placental perfusion. Therefore, it is crucial from a clinical standpoint to prevent and treat maternal spinal hypotension effectively. Sympathetic block resulting in peripheral vasodilation is cited as the main mechanism leading to a decrease in systemic vascular resistance (SVR).[2] SA also decreases splanchnic blood flow by approximately 20%. The resulting splanchnic hypoperfusion releases emetogenic factors such as serotonin from the gastrointestinal tract. Also, acute sympathetic blockade may cause unopposed vagal action and subsequent hyperactivity in the gastrointestinal tract.[3]

The use of prophylactic vasopressor reduces the incidence of intraoperative nausea and vomiting induced by hypotension. Vasopressors nullify the primary physiological derangement induced by sympathetic blocks, like arteriolar vasodilatation, decrease systemic vascular resistance, and also maintain vascular tone in venous and splanchnic vessels thereby maintaining venous return and cardiac filling.[4] However, one of the biggest problems in obstetric anesthesia is still determining the best course of action to take to

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achieve hemodynamic stability during SA for a CS.

The preferred vasopressor for the management of post-spinal hypotension (PSH) during CS is phenylephrine (PE), although ephedrine and mephentermine are widely used as a vasopressor.[3] It has immediate onset and moderate duration of action on the direct α1 receptor, causing baroreceptor-mediated bradycardia, which subsequently lowers cardiac output. It is a sympathomimetic amine that causes arteriolar vasoconstriction to raise mean blood pressure and systemic vascular resistance. It is less likely to cause neonatal acidosis than ephedrine while still maintaining uteroplacental blood flow.[5]

Noradrenalin or norepinephrine (NE) has potent α 1 and modest β receptor agonist effects leading to significant vasoconstriction with some direct inotropic effects. Its administration leads to higher heart rates than comparable doses of PE. However, its role is mostly limited in septic shock intensive care units (ICU) and OTs with hypovolemic shock. Recently, NE has been tried as a possible alternative to PE in controlling maternal hypotension under SA.[5]

When compared to relying solely on rescue dosing, prophylactic continuous infusion with rescue bolus dosing improves hemodynamic stability while decreasing clinician workload and improving maternal comfort. The null hypothesis of our study is that there is no difference in the hemodynamics following SA in elective CS when a prophylactic infusion of NE or PE is used. The current study aimed to compare the effectiveness of PE and NE infusions in patients undergoing elective CS under SA.

Methods

It was a randomized clinical trial conducted in the obstetrics operation theatre under the department of anaesthesiology and critical Care, Guwahati Medical College and Hospital, Guwahati for one year from 1st August 2021 to 31st July 2022, with prior permission and approval from the Institutional Ethics Committee (No. MC/190/2007/Pt-11/July-2021/TH-20). Our study included parturient of the American Society of Anesthesiologists (ASA) physical status I and II, aged between 18 to 40 years old, with a gestation of 37 weeks or more, uncomplicated, pregnant women undergoing elective CS under SA. Patients with ASA≥ II, multiple pregnancies, premature rupture of membrane, pregnancy-induced hypertension (PIH), antepartum hemorrhage (APH), patients in active labor, diabetes mellitus, ischemic heart disease, cerebrovascular disease, hepatic and renal disease, and patients contraindicated for spinal anesthesia were excluded from the study.

One sixty-four patients were randomized into 2 groups following computer-generated random numbers using a randomizer website and allocated with a concealed envelope. Patients were divided into two groups; Group N (n=82) and Group P (n=82). Group N (n = 82): Received NE infusion at the rate of 0.05 µg/kg/min. Group P (n=82): Received PE infusion at the rate of 0.75µg/kg/min. The research substance was kept blinded by the patients and the attending anaesthesiologists. The research medicine was given as vasopressor infusion after subarachnoid block according to the allocated study groups:

Primary outcome: Incidence of PSH (post-spinal hypotension).

Secondary outcome:

- Incidence of severe post-spinal hypotension (SPSH).
- Total vasopressor rescue bolus doses required.
- Number of physician interventions.
- Apgar score at 1 and 5 minutes.
- Nausea and vomiting.
- Incidence of reactive hypertension (RH).

All parturients were visited the night before the study and explained about the study. Written and informed consent was taken. The patients were kept nil orally for 6hrs. All of the patients were given intravenous (IV) injections of pantoprazole 40 mg and metoclopramide 10 mg intramuscular (IM) as premeditated. In the operating room, standard monitoring devices such as a pulse oximeter, non-invasive blood pressure (NIBP), and electrocardiogram (ECG) were connected. The baseline NIBP and heart rate (HR) were measured and recorded. SA was performed at the L2-L3 or L3-L4 vertebral interspace with the patients in lateral decubitus position with a 25 G Quincke needle (Spinocan® G25) under all aseptic precautions and 2.5- 3 mL hyperbaric bupivacaine (bupivac heavy) with injection buprenorphine 0.2ml (60 µg) at a rate of 0.2 ml/sec was administered as per our institutional protocol after a free flow of cerebrospinal fluid (CSF). The patients were then positioned supine with a wedge on their left side. Block success was assessed after intrathecal injection using the pinprick method. Supplemental oxygen was given through a facemask at a flow rate of 3 liters/min. After obtaining T6–T4 sensory level to pinprick, surgery was allowed to proceed. Co-loading was performed with crystalloid solution (Ringer lactate) at the rate of 20 mL/kg which was divided

into two halves. The first part (10 mL/kg) was given before and the second half (10 mL/kg) was infused after spinal anesthesia. After subarachnoid block (SAB), patients received the vasopressor infusion according to the allocated study groups. The vasopressor was infused in the same line with IV fluids using a three-way cannula. The junior resident who was not involved in the study administered the SAB did an intraoperative and postoperative assessment of the patient's parameters and started infusions of the study drugs to the patient as per group allocation.

In case of failure to achieve adequate spinal block or block failure, the patient was converted to general anesthesia and study drug was discarded and excluded from the study. The patient received 10 IU of oxytocin in 500 ml of normal saline (0.9% NaCl solution) IV (150 mL/hour) and 10 IU of oxytocin IM after delivery of the anterior shoulder.

After the administration of SAB, the following parameters were noted:

- Haemodynamic of the patient till 60 minutes.
- Episodes of hypotension, RH, and bradycardia.
- Total number of vasopressor bolus used.
- Maternal side effects like nausea, vomiting, and chest discomfort.
- Apgar score at1and 5 minutes.

Hemodynamic parameters were defined and managed accordingly as follows.

Post spinal hypotension (PSH) was defined as a combination of two criteria, i.e. systolic blood pressure (SBP) ≤ 100 mmHg, or < 80% baseline. It was corrected by giving a vasopressor bolus. The vasopressor bolus was PE 50µg IV (if the HR>75/min) or IV ephedrine 6mg if HR<75/min). Severe post spinal hypotension (SPSH) was defined as SBP <60% of the baseline reading. It was corrected by administration of either IV PE 100 µg (if HR > 75 /min) or IV ephedrine 15 mg (if the heart rate < 75/min).[3] Reactive hypertension was defined as SBP>120% from the baseline reading. It was managed by the stoppage of the infusion till the next SBP reading. The infusion will be then restarted at a reduced rate (50% of the initial dose) when SBP decreases back within 20% of the baseline reading. Bradycardia (<50/min) was treated with incremental doses of injection atropine 0.3mg. Physician intervention was defined as any of the following as vasopressor bolus, atropine bolus, cessation, restarting, and changing of the vasopressor infusion rate.

The sample size was calculated using G-Power 3.1.9.7 statistical software. The sample size required for this study was estimated from a previous study which demonstrated an incidence of PSH in the PE group was 32% and in the NE group 30% with an effect size of 0.23 [4]. Based on $\alpha = 0.05$, $\beta = 0.20$, and a mean difference of 20%, with an estimated standard deviation of 20±5.7, a sample size of 75 per group was required. Considering an attrition rate of 10%, 82 patients in each group were included in this study.

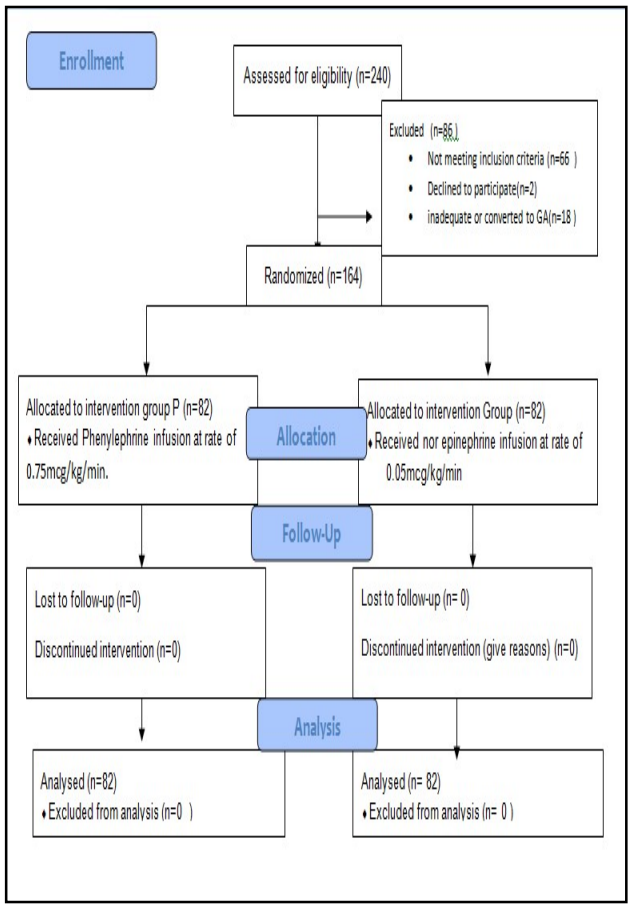

Figure 1: Consort flow diagram

A total of 240 patients were assessed for eligibility, out of which 86 patients were excluded from the study. Sixty-six patients were excluded from preoperative visits due to not meeting inclusion criteria. Eighteen patients had an inadequate block or were converted to general anesthesia. Two patients declined to participate and were therefore excluded from the study. A total of 164 patients were enrolled in our study, with 82 numbers of patients in each group (figure1).

Statistical analysis: The data were entered into Microsoft Excel spreadsheets. The description of the data is in the form of mean ± SD for quantitative data while in the form of % proportion for qualitative (categorical) data. Chi-square and Fisher's exact test were used to evaluate the association between categorical variables. Data were checked for normality using Kolmogorov-Smirnov and Shapiro-Wilk tests. Within the same group, the dependent t-test was used to compare the mean difference. The unpaired t-test was used to compare the mean difference between the two independent groups depending on the fulfilment of the normality assumption for continuous variables. For non-normal data Mann-Whitney test was used. The statistical analyses were done using PSW software version 21.0. A p-value < 0.05 is considered significant.

Results

The patient characteristics are shown in table 1. There was no statistical difference between the two groups in demographic data. Duration of operation, baseline HR, SBP, DBP, and MAP were not statistically different either.

Table 1: Demographic variables

Demographic variables	Group P	Group N	P-value
Age (yr)	24.98±2.90	25.04±3.44	0.929
Height (cm)	151.1 ± 6.3	153.3 ± 4.3	0.469
Weight (kg)	71.0 ± 12.5	66.3 ± 12.3	0.291
ASA I/II	53/2	52/3	0.93
Body mass index (kg/m^2)	27.7 ± 3.9	26.4 ± 4.5	0.39
Operation time (min)	45.9 ± 13.5	41.4 ± 14.1	0.354
Baseline HR (beats/min)	81.02±7.51	84.93±13.17	0.058
Baseline SBP (mmHg)	120.98±7.89	121.04±6.86	0.969
Baseline DBP (mmHg)	74.65±5.45	76.29±7.04	0.176
Baseline MAP (mmHg)	90.09±5.88	90.58±6.06	0.667
Baseline SPO2 (%)	99.35±0.58	99.49±0.57	0.19

SD = Standard deviation; ASA=American Society of Anesthesiologists; SBP=Systolic blood pressure; DBP= Diastolic blood pressure: MAP=Mean arterial pressure.

Hemodynamic parameters were measured at the start and at fixed time intervals for 60 mins. The mean HR was comparable between the two groups (p-value > .05) (figure 2). The mean SBP, DBP, and MAP were comparable between the two groups (p-value >.05) (figure 3). The incidence of PSH was 24% (n=20) and 29.26% (n=24) in group P and group N respectively. There was no statistically significant difference between the groups (p-value > 0.05) (table 1). The incidence of SPSH in group P was 3.6% (n=3) while in group N was 2.4% (n=2). There was no statistically significant difference between the groups (p-value > 0.05) (table 2). No of bolus dose of vasopressor required between the two groups was comparable and there was no statistically significant difference between the groups (p-value > 0.05) (table 3). Reactive hypertension was noticed in both groups, 14.20% (n=12) and 7.30% (n=6) in group P and group N respectively. There was no statistically significant difference between the groups (p-value > 0.05) (table 4).

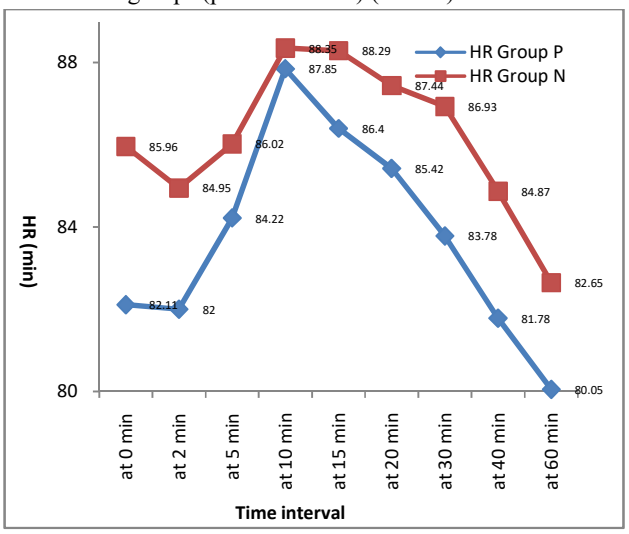

Figure 2: Comparison of HR variation between the groups

Table 2: Comparison of maternal outcomes between the groups

Maternal outcomes	Group P		Group N		P value
	N	%	N	%	
PSH	20	24%	24	29.26%	0.62
SPSH	3	3.60%	2	2.40%	0.65
Total number of vasopressor bolus used					
1	18	21.90%	14	17.07%	
2	2	2.43%	2	2.43%	0.531
≥3	0	0%	1	1.20%	
Reactive hypertension	12	14.20%	6	7.30%	0.122
Nausea and vomiting	7	8.50%	9	10.90%	0.588
Bradycardia	6	7.30%	3	3.65%	0.296
No of physician intervention	32	39.02%	23	28.04%	0.0257

N=number; %= Percentage; PSH=Post-spinal hypotension; SPSH=Severe post spinal hypotension.

Table 3: Comparison of Apgar score at min1 and min5 between the groups.

Apgar Score	Group P N (%)	Group N N (%)	P value
At 1 minute			
≤7	6 (7.31%)	4(4.87%)	>.05
>7	76(92.68%)	78(95.12%)	1
At 5 minutes			
≤7	0	0	1
>7	82(100%)	82(100%)	1

The occurrence of nausea and vomiting was very low in both groups and was comparable. Patients in both groups developed bradycardia and were comparable (p-value > 0.05) (table 2). The number of physician interventions needed in group P (39.02%) was significantly higher compared to group N (28.04%). (p-value < 0.05) (table 2].

The Apgar score of the babies was measured at min1 and min 5 in both groups and was comparable. There was no statistically significant difference between the groups (p-value > 0.05) (table 3).

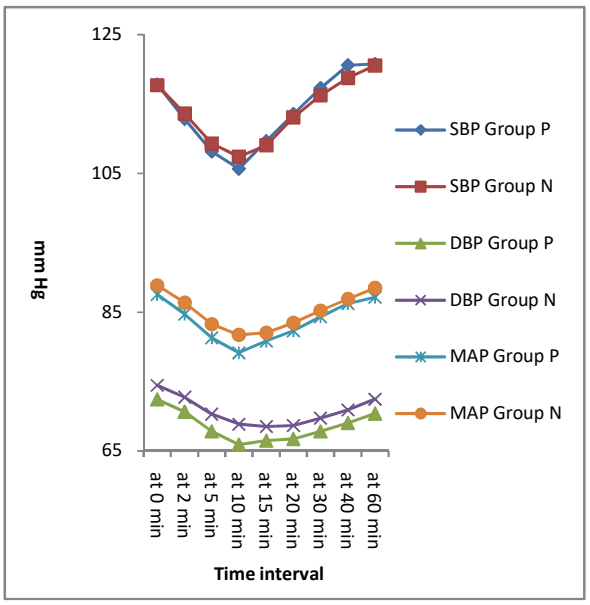

Figure 3: Comparison of SBP, DBP, and MAP variation between the groups

Discussion:

Many studies in patients have shown PE to be effective and have a potent direct a_1-effect, with no β-effects at clinical doses, and have demonstrated that PE is the best choice of vasopressor in obstetrics anesthesia. However, when higher than required doses administered; it may induce baroreceptor-mediated bradycardia with a consequent reduction in maternal cardiac output. NE being a potent α_1-adrenergic agonist, with modest β-agonist activity, causes marked vasoconstriction with some direct inotropic effects resulting in higher heart rates than with comparable doses of PE.[5] So, in our study, the primary outcome was to evaluate the effect of PE and NE infusion for prophylaxis of PSH in patients undergoing CS under SA.

The results of our study showed that NE had similar efficacy for maintaining blood pressure compared with PE during SA for CS. The mean SBP observed in our study in group P and group N was not statistically significant. The incidence of PSH in group P was 24% (n=20) while in group N was 29.26% (n=24) and comparable. None of the previous studies done in patients undergoing elective CS had shown a significant difference in the systolic blood pressure between the use of PE and NE infusion for preventing PSH. A study conducted by Cho WJ et al compared the effects of NE and PE used as intermittent boluses in elective CSs under SA. They assigned groups to receive either intermittent bolus dosing of PE (100 g/ml) or NE (5 g/ml). They discovered significant within-group differences in the SBP, HR, and SVR.[6]

We observed a very low incidence of SPSH in our patients in groups, 3 patients (3.6 %) in group P and 2 patients (3.6%) in group N. The finding was statistically insignificant and comparable to Hasanin A et al, wherein they found the occurrence of SPSH statistically non-significant as the doses they used were comparable with our study.[7] No other relevant study has been found to evaluate SPSH. In our study, we also evaluated the incidence of bradycardia between the two groups intraoperatively. The incidence of bradycardia was 8.50% (n=7) and 10.90% (n=9) in group P and group N respectively and were comparable. This finding of our study was consistent with the studies of Hasanin A et al and Vallejo MC et al where they used both drugs as an infusion.[7,8] In a study conducted by Mohta M et al comparing the effects of 100 µg PE and 5 µg NE administered as boluses used for the treatment of PSH during elective CS comparing the incidence of maternal bradycardia. They found no statistically significant differences in the incidence of bradycardia stating the fact of using the bolus technique and administering low doses.[9] However, studies done by Osmani et al, Wang X et al, Abdelmaboud MA et al and Sharkey AM et al showed that the incidence of bradycardia was significantly lower in the NE group in comparison to the PE group.[10–13] It may be attributable to the fact that the drugs were given as bolus doses and not as infusions.

Chen Z et al. conducted an RCT in 100 parturients with twin gestation undergoing CS with SA where they found a significant difference in the incidence of bradycardia, lower in the NE group.[14] The probable reason behind this finding might be that the vasopressor was infused at a fixed rate for all the patients, instead of manually adjusted infusion nor closed-loop feedback computer-controlled infusion and the study population consisted of twin gestation.

Ngan Kee WD et al conducted an RCT on healthy patients scheduled for CS under SA to compare computer-controlled infusions of PE (0–100µg/min) and NE (0 – 5µg/min) used to maintain arterial blood pressure. They found that the incidence of bradycardia was lower in the NE group compared with that of the PE group.[4] The cause of this

heterogeneity may be due to the higher dosage of the PE considered in their study as they compared NE at a concentration of 5 µg/ml versus PE at a concentration of 100 µg/ ml according to their estimate of a potency ratio of 20:1; However, they found that the median infusion rate required to maintain blood pressure was greater in the NE group. They concluded that the true potency ratio for NE:PE for maintaining blood pressure under the conditions of their study is probably less than 20:1, whereas, in our study, we used NE and PE infusions at a potency ratio of 15:1.

There was no significant difference in the total number of rescue bolus doses of vasopressor in both the groups in our study. This finding of our study is consistent with the findings of Vallejo MC et al.[8] It may be due to the fact that the patients received PE infused at a rate of 0.1 µg/kg/min and NE infused at a rate of 0.05 µg/kg/min which was comparable to our study. Geol et al also found no statistically significant difference in usage of rescue boluses for the treatment of hypotensive episodes which is attributable to the fact that the patients in both groups were receiving prophylactic doses of NE and PE.[15] Our findings were inconsistent with Mohta M et al where the total numbers of boluses used were significantly higher in the PE group.[9] Puthenveettil et al conducted a study comparing NE and PE boluses for the treatment of hypotension during SA for CS, with group P receiving PE 50 µg and group N receiving 4µg of NE respectively as IV bolus to treat spinal hypotension. The number of boluses of vasopressor required to treat hypotension was significantly lower in group N.[16] This might be attributable to the fact that both these studies used bolus doses of study.

The Apgar score at 1 minute and 5 minutes in our study were comparable between the groups. This finding of our study was consistent with the findings of Vallejo MC et al, and Ngan Kee et al.[4,8] The occurrence of reactive hypertension in both groups was also compared in our study and no significant difference was found between the two groups. This finding was found to be consistent with Mwaura L et al, Mohta M et al, and Hasanin A et al.[7,9,17] It might be due to the fact that the doses in these studies were comparable with our study. Jaitawat SS et al found significant reactive hypertension when using PE 100 µg as a bolus in comparison to PE 75 µg bolus in his trial. In our study infusion was used instead of a bolus.[18]

In our study, we also compared the incidence of nausea and vomiting in both study groups. There was no significant difference in terms of nausea and vomiting between the two groups. Only 7 patients in group P and 9 patients in group N developed nausea and vomiting. Our findings were consistent with Goel et al and Hasanin A et al.[7,15]

In our study, there was a statistically significant difference found in the physician interventions that were required between the two groups. This finding of our study was consistent with the findings of Hasanin A et al who also found a significant difference in physician interventions required between the groups.[7] This might be attributable to the fact that doses for infusion of the study drugs were similar in both studies. Chen Z et al conducted an RCT in 100 parturients with twin gestation undergoing CS with SA. They were randomized to receive prophylactic NE (3.2µg/min) or PE infusion (40µg/min). They found that the requirements of physician interventions to correct maternal hemodynamic abnormalities were similar in both groups.[14] This inconsistency might be due to the fact that they used 2.5ml of 0.5% isobaric bupivacaine for SA without any opioids adjuvant with the patient in the left lateral position and measured blood pressure until the delivery of the second baby.

In our study, we decided to use an infusion of vasopressor to prevent hypotension. Many studies have recommended the use of prophylactic infusions of the drug PE and NE for PSH. Infusions of PE and NE were effective in decreasing the incidence of hypotension and resulted in more stable BP control compared with a control group that received rescue boluses of the above-mentioned drugs. Also, it offers the advantage of limiting clinician workload and increasing maternal comfort. In our study, we gave prophylactic infusions to the patients based on weight as it was found that the incidence of hypotension was significantly less than in the weight- adjusted intervention group in comparison with the fixed-dose control group.[5]

Limitations: It is a single-hospital study, but a multi-hospital study is considered to be better. Our study population was not large enough to assess the difference in the occurrence of adverse effects and postoperative nausea and vomiting. Umbilical arterial blood gas analysis was not performed in our study to evaluate the neonates' biochemical abnormalities due to the effect on cardiac output. We excluded pregnant women with uteroplacental insufficiency and fetuses with intrauterine growth retardation.

Conclusion

Hemodynamics in patients undergoing elective CS was comparable when PE or NE infusion was used to prevent hypotension following SA. NE is associated with a lower

number of physician interventions as compared to PE in patients when administered for the prevention of PSH undergoing elective CS.

Conflict of interest: None. **Disclaimer:** Nil.

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