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Research Article

A Prospective Randomized Double Blind Comparative Study to Determine the Efficacy of Norepinephrine and Ephedrine to Maintain Arterial Blood Pressure During Spinal Anesthesia for Cesarean Delivery

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ABSTRACT

Background: Spinal Anesthesia Induced Hypotension(SAIH) continues to be the troublesome complication for obstetric patients undergoing cesarean section under subarachnoid block. Vasopressors are emerging as the cornerstone of treating SAIH in cesarean section patients with the evolving evidence of arterial vasodilatation as the primary cause of hypotension. This study was hypothesized to compare the efficacy of norepinephrine and ephedrine boluses to maintain hemodynamics in cesarean section.

Methods: After approval from institutional ethics committee and registration in Clinical Trials Registry India(CTRI) and informed consent, study was conducted in 110 healthy parturients aged 18-40 years, belonging to ASA physical status I and II, posted for elective cesarean section under spinal anesthesia, were randomly allocated into group N(n=55) and group E(n=55),who received intravenous boluses of norepinephrine 6 □g and ephedrine 10mg respectively as prophylaxis(one dose soon after induction) and in treatment of SAIH. The number of vasopressor boluses were recorded as primary objective and hemodynamics, APGAR scores, adverse events were noted.

Results: The number of boluses of vasopressor used was 1.9±1.2 for Ephedrine and 4.72±2.9 for Norepinephrine. At 30,40,50 and 60 minutes after anesthesia, there was significant fall in mean arterial pressure in the norepinephrine group compared to ephedrine group. The incidence of tachycardia was more in ephedrine group and incidence of bradycardia was more in norepinephrine group.

Conclusion: Both the study drugs, ephedrine and norepinephrine are comparably effective in preventing SAIH after prophylactic bolus and effective in maintaining blood pressure intraoperatively, more number of boluses of norepinephrine was required compared to ephedrine.

Introduction

The most popular anesthetic technique for cesarean delivery is spinal anesthesia [1]. But associated hypotension continues to be a problem as, cesarean sections require an anaesthetic block upto T4 level and incidence of hypotension can be as high as 80% [2].

Severe and sustained hypotension can be detrimental to both mother (nausea, vomiting, dizziness) and fetus

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(impairment of placental blood flow with consecutive fetal hypoxia, acidosis and neurological injury) [3].

Several interventions (Crystalloid or colloid pre loading or co-loading, vasopressors, leg elevation, leg wrapping, low spinal anesthesia) have been tried, either alone or in combination with varied success [4]. Vasopressors have always been the preferred intervention, with ephredrine and phenylephrine, which stood the test of times, remain the first choices of obstetric anaesthesiologist [5]. However, in the recent years, Noradrenaline (which is the first choice of vasopressor in intensive care unit and sepsis) has been tried in treating obstetric hypotension, both as boluses or infusion [6]. Norepinephrine, being a weak β-adrenergic and potent α-adrenergic agonist, norepinephrine may be a better option for maintaining maternal blood pressure because it has less of a negative impact on heart rate and cardiac output [7-9].

We hypothesized the present study to determine the effectiveness of nor epinephrine in maintaining maternal blood pressure compared to ephedrine during cesarean section under spinal anaesthesia.

Methods

After obtaining institutional ethics committee approval, registration in Clinical Trials Registry of India (REF/2020/12/036361) and informed consent, study was conducted on 110 healthy parturients aged 18-40years, belonging to ASA (American Society of Anaesthesiologists) physical status I and II, with singleton pregnancies at term, posted for elective cesarean section under spinal anesthesia at a tertiary care teaching hospital over a period of one year from December 2020 to December 2021.

Since no study could be located in the literature at the time of the study period employing the same dosage in relation to the primary goal of the total number of boluses administered in the two groups, a pilot study was conducted with 8 patients in each group and based on the mean and the standard deviation sample size was calculated. The pilot study data indicates that mean (SD-standard deviation) number of boluses in two groups Norepinephrine and Ephedrine were 3.13 (1.64) and 3.25 (1.58) respectively. To be able to reject the null hypothesis that the difference in number of boluses of vasopressors between the two groups is zero with probability (power) 0.80 and type I error probability of 0.05, a minimum of 48 subjects in each group (Total 96) required. Considering dropouts, a final total sample of 110 subjects were studied with 55 in each group.

The study excluded pregnant women with foetal anomalies, ephedrine or norepinephrine allergies or hypersensitivity, heights greater than 180 cm, BMIs greater than 40 kg/m2, hypertensive disorders of pregnancy, and cardiovascular or cerebrovascular illness.

The primary objective of our study was to compare the number of intravenous bolus doses of Norepinephrine or Ephedrine required to treat spinal hypotension in caesarean patients. The secondary objectives were, the incidences of bradycardia, tachycardia, hypertension, hypotension, maternal nausea and vomiting and fetal outcomes such as APGAR score.

Preoperative evaluation of all the patients was performed a day before surgery with detailed history, physical examination. All patients were advised to be nil per oral as per current ASA guidelines. Aspiration prophylaxis, Ranitidine 150 mg and Metoclopramide 10 mg was given orally on the night before surgery and two hours prior to surgery. The parturients were allocated into two groups by computer generated random numbers and allocation concealment was done by serially numbered closed envelopes placed in a container. Norepinephrine and ephedrine were diluted and loaded in an identical coded 10-mL syringe to give Norepinephrine 6 μg/mL and ephedrine 10 mg/mL. The study drug preparation was done by an anesthesiologist who was not involved in investigation of study. An 18G intravenous access was secured. The monitoring was done with noninvasive multiparameter monitor which included pulse-oximeter (Spo2), noninvasive blood pressure (NIBP) and electrocardiogram (ECG).

With the patients in the sitting position, under strict aseptic precautions, lumbar subarachnoid block was performed at L3–L4 or L4–L5 level using standard technique with 2ml of 0.5% hyperbaric bupivacaine (Anawin) given slowly over 15 second using 25-G Quincke Babcock spinal needle after confirming free flow of CSF. Then the patients were made to lie supine with a wedge under the right buttock. The time of institution of subarachnoid block was noted. They were co-loaded with 10mL/kg of lactated Ringer's solution. Supplemental oxygen was given through facemask at a flow rate of 6 L/min.

1.Group N (n=55) received a prophylactic bolus of Norepinephrine 6 μg intravenously at the time of intrathecal block, plus boluses of Norepinephrine 6 μg, whenever maternal systolic blood pressure (SBP) dropped by 20% or more from baseline value. 2.Group E(n=55) received a prophylactic bolus of Ephedrine 10mg intravenously at the time of intrathecal block, plus boluses of 10mg Ephedrine, whenever maternal systolic blood pressure (SBP) dropped by 20% or more from baseline value.

The highest level of sensory blockade achieved was assessed with pin prick 5 minute after intrathecal injection and patients with failed block were excluded from the study. Surgery was started when the sensory level of block reached T6 dermatome. The patient and the investigator were blinded to the vasopressor used. Blood pressure and heart rate were monitored 1st minute and then every 3 min till 10 min, and thereafter every 5 min till the end of surgery. The number of boluses of vasopressor required and episodes of hypotension were recorded. After delivery of baby, 10U of oxytocin was given as a slow infusion. Attending pediatrician noted APGAR score at 1 and 5 min. The time of skin incision,

uterine incision and the delivery of the baby were noted down. Any adverse events like nausea, vomiting, headache or dizziness were noted.

Statistical Analysis

Data was entered into Microsoft excel sheet and was analyzed using software SPSS 22. Categorical data was represented in the form of frequencies and proportions. Chi-square test was test of significance. Continuous data was represented as mean and standard deviation. Mann-Whitney U test, unpaired t-test, Wilcoxon Rank sum test, Chi square test, and Fischer's exact test were used to find out possible associations. P value of less than 0.05 considered significant.

Results

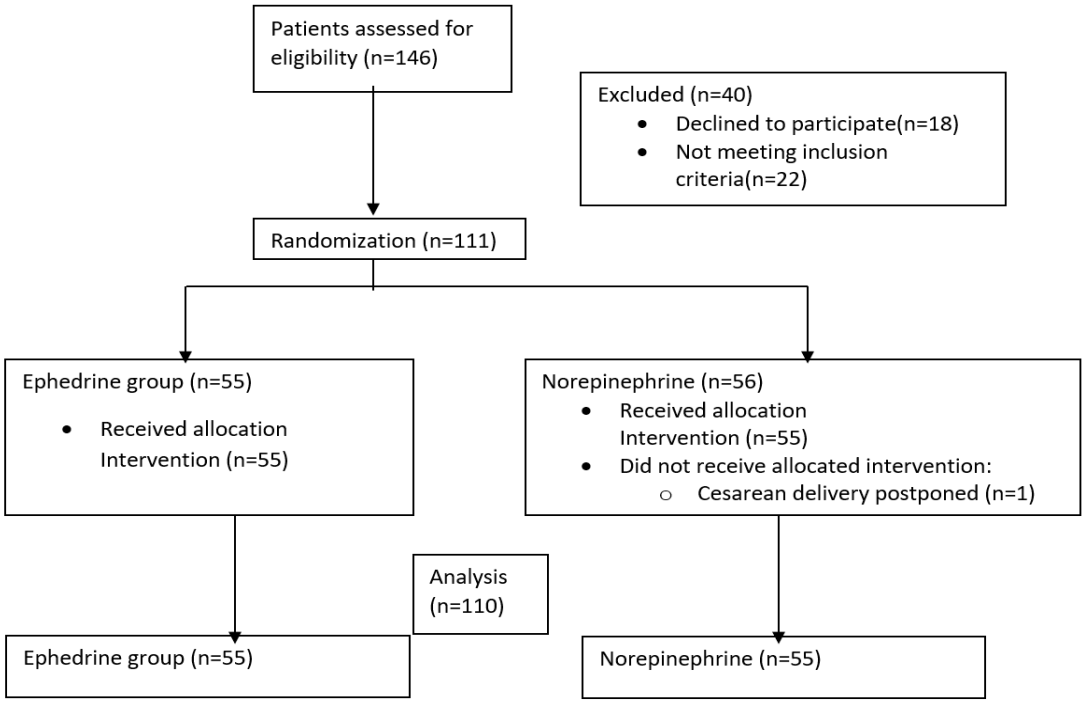

Figure 1- Consort Diagram

The study involved 110 healthy parturients belonging to ASA physical status I and II posted for caesarean section under spinal anesthesia. They were randomly allocated in to either Group E (Ephedrine group) or Group N (Norepinephrine group).

Demographic data of parturients, level of spinal blockade, volume of fluids infused, duration of incision to delivery interval and duration of surgery were statistically comparable between the two groups (Table1).

The incidence of hypotension was 41/55 in ephedrine group and 43/55 in Norepinephrine group (Table 2).

The average frequency of hypotension therefore the number of boluses of vasopressor used was 1.9±1.2 for Ephedrine and 4.72±2.9 Norepinephrine. There was a fall in the blood pressure in both the groups after the administration of spinal anesthesia. The fall in Systolic blood pressure was significantly more in noradrenaline group at 3rd, 7th, 10th, 15th, 20th, 25th, 30th, 35th, 40th, 45th, 50th minutes compared to ephedrine group after spinal anaesthesia. The fall in diastolic blood pressure was statistically significant in Norepinephrine group at 15th,20th,25th,30th ,40th,50th ,60th minute compared to ephedrine group. At 30, 40, 50 and 60 minutes after anesthesia there was significant fall in mean arterial pressure in the Norepinephrine group compared to ephedrine group (Figure 2). There was significant increase in heart rate (soon after prophylactic dose) after 1 minute of induction with spinal anesthesia in Ephedrine group and was persistent throughout the surgery (Figure 3). The incidence of tachycardia was significantly more in Ephedrine (33/55) group (Table 3). The incidence of bradycardia was more in Norepinephrine (25/55) group. There was no difference between the groups in the prevalence of reactive hypertension (Table 3).

It was noted during surgery that Norepinephrine caused transient bradycardia soon after administration of bolus which subsided within a minute. APGAR score at 1 minute and 5 minutes were similar in both the groups. The occurrence of nausea, vomiting, and dizziness in pregnant women were infrequent in both groups. One and two parturients developed nausea and dizziness in Ephedrine and Norepinephrine group respectively, one parturient in each group had an episode of vomiting.

Table 1- Demographic data and operative details

Parameters	Ephedrine Group (n=55) (mean±SD)	Norepinephrine Group (n=55) (mean±SD)	P value
Age(yrs)	25.45±4.04	25.61±3.87	
Weight(kg)	57.47±9.45	58.92±7.20	>0.05
Height(cm)	156.56±4.29	156.6±4.30	
Level of block	T6(median)	T6(median)	
Volume of fluid infused (ml)	1500±30ml	1500±30ml	
Time from skin incision to delivery of baby (minutes)	5.34 ±2.45	5.64 ±2.57	0.536*
Duration of surgery(minutes)	51.5 ±11.6	53.1 ±8.8	0.547

* unpaired t-test. # Wilcoxon Rank sum test. (P value<0.05 was considered significant)

Table 2- Incidence and frequency of hypotension

Group	Nor adrenaline group	Ephedrine group
Incidence of hypotension	41/55	43/55
Number of boluses of vasopressor required (mean±SD)	4.72±2.97	1.9±1.2

Table 3- Maternal hemodynamics and neonatal outcomes in percentage

Parameters	Ephedrine-n(%)	Norepineprhine-n(%)	(chi square/Fisher's exact test) p value
Incidence of hypotension	41(74.5%)	43(78.2%)	0.654
Incidence of tachycardia	33(60.0%)	4(7.3%)	<0.001
Incidence of bradycardia	2(3.6%)	25(45.5%)	<0.001
Incidence of hypertension	10(18.2%)	5(9.1%)	0.165
APGAR at 1 MIN	8(14.5%)	11(20.4%)	0.423
APGAR at 5 MIN	1(1.8%)	2(3.7%)	0.547

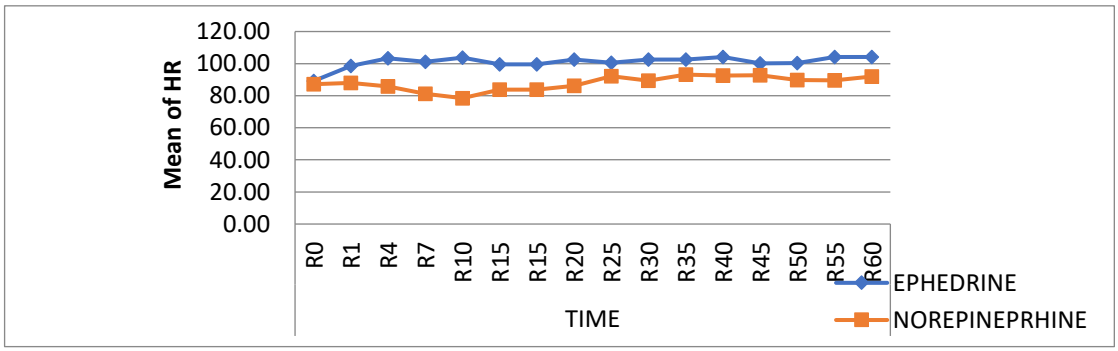

Figure 2- Graph of Mean MAP (mean arterial pressure) versus time

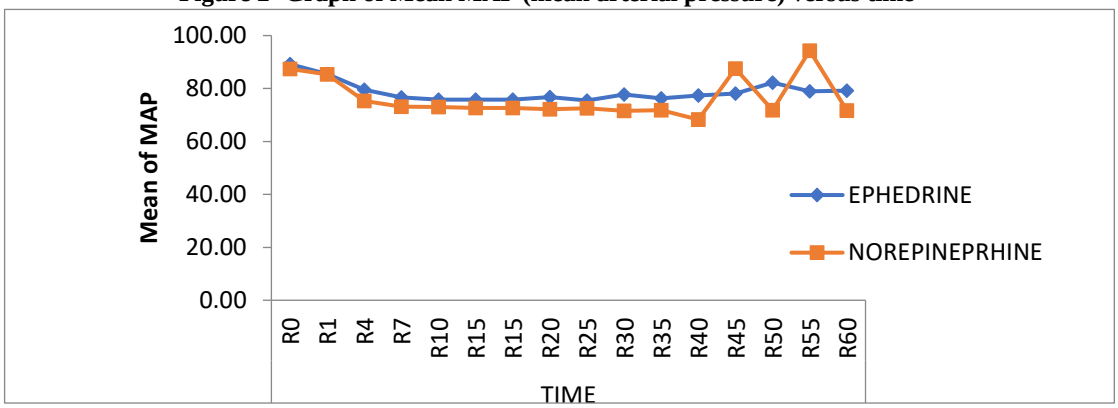

Figure 3- Graph of Mean MAP (mean arterial pressure) versus time

Discussion

The results of the present study show that both the study drugs, Noradrenaline and ephedrine are effective in treating Spinal Anaesthesia induced Hypotension(SAIH) in obstetric patients undergoing cesarean section, even though the number of boluses needed to sustain hemodynamics is more in norepinephrine group. There was increase in the heart rate in ephedrine group and transient decrease in the heart rate in the noradrenaline group after bolus.

Subarachnoid block remains the most popular technique for cesarean section, to avoid airway complications and neonatal respiratory depression associated with general anesthesia [10]. Due to its safety in pregnancy, simplicity and low dose of drug needed, adequate muscle relaxation, low placental transfer of drug, awake state of mother for maternal-infant bonding and early initiation of breast-feeding, improved postoperative analgesia, quicker return of gastrointestinal functions following surgery, early mobilization, it is the preferred choice of anesthesia for caesarean section [10].

Spinal anesthesia has its own set of adverse effects, the most common being hypotension, seen in 80% of the patients which is due to sympathetic blockade after its administration [11].

According to the traditional view point, the decrease in venous return and cardiac output brought on by sympathetic blockade is the one that induces the hypotension. The measures to increase the venous return (intravenous fluid loading and volume expansion, compression or lifting of legs) have largely been ineffective in managing SAIH in parturients. According to a growing body of research, spinal hypotension is predominantly brought on by a reduction in sympathetic tone in the arterial system rather than an increase in venous capacitance or a decrease in venous return [12]. That is the reason, the role of vasopressors has assumed greater importance in treatment of SAIH in the recent times. However, the choice of vasopressor to maintain normotension in this scenario has been debated for a long time [12]. Various vasopressors have been used for prevention and treatment of SAIH namely Metarminol, Mephenterimine, Ephedrine, Phenylephrine and recently Norepinephrine either as boluses or infusions [5,12].

Ephedrine was traditionally thought of as the best drug to keep blood pressure normal [13]. Due to its safety, accessibility, and familiarity among anesthesiologists, ephedrine is commonly utilised [14]. It maintains cardiac output by acting indirectly by releasing norepinephrine, which increases heart rate and myocardial contractility [15]. It also causes peripheral vasoconstriction by directly acting on α and β receptors hence it raises blood pressure [16]. Its vasoconstriction impact is diminished with repeated administration, and its slower onset and prolonged duration of action make it less attractive for titrating blood pressure effects [17-19]. Ephedrine was shown to have slower onset of action (2-3 minute) compared to Norepinephrine which acts within 60 seconds.

In contrast to α agonists like phenylephrine, recent trials have revealed norepinephrine to be a promising medication in SAIH for sustaining normotension with minimal deleterious effects on cardiac output and heart rate [8,11,20]. Norepinephrine has potent alpha and weak beta agonistic activity therefore fewer negative effects on heart rate and cardiac output [17]. Therefore, Norepinephrine has both reflex negative chronotropic action as well as direct positive chronotropic action with overall effect on the heart rate considered to be normal [11]. Direct α1 receptor stimulation causes intense vasoconstriction with increase in MAP and SVR. Also, venoconstriction increases venous return to the heart. Recent literature states that the time of onset of action for Norepinephrine is less than 60 seconds [17].

A study by Onawochei et al. who compared various doses of Norepinephrine, 3, 4, 5, 6, 7, 8 µg, shows that ED90 of an intermittent bolus of dose of Norepinephrine is 5.8 µg (95% CI, 5.01-6.59 µg) for prevention of spinal hypotension [21]. It was easier to administer and was effective in 19/20 patients receiving the dose. For practical use 6 µg was recommended and therefore this dose was chosen for the present study [21]. Elnabtity et al. did a comparative study between Norepinephrine 5 µg and Ephedrine 10 mg [17]. Considering these two studies we chose the dose of the drugs to be Norepinephrine 6 µg and Ephedrine 10 mg. But recent studies show that equipotent dose of 6mcg of Norepinephrine to be 6mg of Ephedrine as the potency ratio is 1:1000 [17,21].

The theoretical concerns regarding the use of Norepinephrine leading to peripheral tissue ischemia has not been supported by evidence. A recent study with peripheral Norepinephrine infusion at a rate of 30 mcg/min in hypotensive patients for an average of 32 hours showed no morbidity via 18-20 –gauge cannula22. In the present study, Norepinephrine boluses were used and the crystalloid was continuously on flow, no such adverse consequences were observed.

In the present study, requirement of Norepinephrine boluses was more compared to Ephedrine (4.72±2.97 versus 1.9±1.2). In a similar study, Norepinephrine was found to be having increased number of boluses requirement, in comparison with Mephenteramine as found by Shah PJ et al [12] (maximum number of patients required 3 boluses versus 1 bolus) and they concluded that it was probably due to its faster onset of action and a shorter half-life of Norepinephrine. Contrary to the findings of our investigation, Elnabtity et al. reported that Ephedrine required more boluses to maintain normotension than Norepinephrine (3 versus 2) did [17].

Few recent studies have shown prophylactic norepinephrine infusion had better hemodynamics during

cesarean section under spinal anesthesia [23-24]. In present study intermittent intravenous bolus was chosen as it is easy, familiar, and cost effective while the preparation of infusion is time consuming and needs equipment like infusion pumps.

In the present study 74.5% in Ephedrine and 78.2% parturient in Norepinephrine group had incidence of SAIH which was comparable among the groups. Shah PJ et al found that hypotension was found in all the parturients involved in the study, therefore excluded it from adverse events [12].

El Shafei [15] et al. conducted a comparative study with 5 mcg Norepinephrine and 5 mg ephedrine to prevent SAIH in patients undergoing arthroscopy of knee as well as in coronary artery disease patients undergoing lower limb orthopedic surgeries respectively. They concluded that Norepinephrine was more efficacious in comparison with Ephedrine in maintaining blood pressure; also, had less incidence of tachycardia which was beneficial in patients with coronary artery disease. This result with respect to tachycardia (significant increase in the heart rate at 5, 10 and 15 minutes after administration of bolus) is in concordance with the results of present study where persistent tachycardia was noted with use of Ephedrine after 1 minute of bolus administration. Similarly less incidence of tachycardia was noted in studies conducted by Xu et al [23], QQ Fan et al [25] and Elnabtity et al [15].

In addition to these results, in the present study, transient bradycardia was noted with the use of Norepinephrine, probably because it has reflex negative chronotropic action decreasing heart rate similar incidence of bradycardia was found in study done by Elnabtity et al [17].

Elnabtity et al [17] compared Norepinephrine with ephedrine for SAIH in parturients undergoing cesarean delivery and found that the maternal heart rate and cardiac output was better compared with Norepinephrine. Even though measuring cardiac output would have been more informative to study the efficacy of Norepinephrine, it was not feasible in the present study. Heart rate thus served as a surrogate marker for cardiac output.

El Shefai et al [15], found no significant reactive hypertension in study conducted with Norepinephrine and Ephedrine as vasopressors following SAIH15. Although prophylactic bolus is related to higher incidence of reactive hypertension, even the present study did not show such results.

QQ Fan et al [25] and Wang et al [26] noted more incidence of IONV in Ephedrine group in comparison to Norepinephrine group, whose findings contrast with present study where no significant difference was found between the groups.

Ephedrine crosses placenta due to its high lipid solubility and therefore can lead to stimulation of beta receptors, increasing fetal metabolism and thereby depressing fetal pH [27], while Norepinephrine does not cross placenta. The main concern with the alpha agonist is the fall in uteroplacental blood flow although few studies have found that Norepinephrine does not alter fetal arterial perfusion pressure and did not compromise fetal microcirculation [28].

According to Elnabtity et al., ephedrine had a slower onset of action. This meant that foetal tachycardia could happen unexpectedly and, in the case of an existing oxygen deficit, could result in foetal acidosis [17]. There was no difference in the APGAR score at 1 and 5 minutes after birth among the groups. Wang et al. found in a study that there was better pH and base excess, bicarbonate and lactate in Norepinephrine group, although it was not statistically significant [26].

The neonatal APGAR score was utilised in this investigation as a stand-in for an indicator of neonatal well-being in the first few minutes of life. No significant difference was found among the groups with respect to neonatal APGAR score. Similar results were seen in other studies as well [12]. Even when umbilical artery pH was assessed for neonatal outcomes, norepinephrine was proved non inferior to phenylephrine [29].

Strengths: The present study is a prospective randomized double-blind study. Norepinephrine is more cost effective and easily available vasopressor. In low-resource environments with few or no infusion pumps, the use of intermittent boluses of the vasopressors may be possible. Also, intermittent boluses are more familiar among most of the anesthesiologists.

Limitations: In the present study, 6 μg and 10 mg were the doses chosen for Norepinephrine and ephedrine boluses but recent studies state that potency ratio of Norepinephrine versus Ephedrine to be 1000:1 [25-26]. Therefore 6mg bolus of Ephedrine would be preferred choice.

Umbilical arterial pH was not analyzed to determine neonatal outcomes. In order to determine how vasopressors affect uteroplacental circulation and newborn outcomes, uterine arterial flow was not assessed.

Heart rate is only a surrogate marker of Cardiac Output(CO). In this study vasopressor was used to maintain the systolic pressure but cardiac output was not monitored. CO monitoring would be potentially more informative.

Conclusion

Ephedrine and Norepinephrine are both effective to maintain blood pressure throughout surgery and to prevent spinal anesthesia-induced hypotension following prophylactic boluses; however, Norepinephrine required more boluses than Ephedrine did.

Ephedrine causes persistent tachycardia whereas Norepinephrine causes transient bradycardia but these variations in the heart rate are not clinically significant enough to cause maternal or neonatal adverse events.

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