Evaluation of the Effect of Norepinephrine, Ephedrine and Phenylephrine on Prophylaxis and Treatment of Hemodynamic Changes Associated with Spinal Anesthesia in Elective Cesarean Section Surgeries

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Abstract

Introduction: As recommended spinal anesthesia is the best technique for planned cesarean delivery. Moreover, it has been stated that vasopressors are more extensively accepted as effective agents in reduction of post spinal anesthesia (PSA) compared to fluid loading. Anyway, there is much debate on the most ideal vasopressor in preventing spinal hypotension during cesarean section. This agent should be capable of maintaining placental perfusion and maternal blood pressure with the least side effects on both fetus and mother. The main objective of the present study was to perform a comparison between prophylactic bolus doses of phenylephrine verses ephedrine and norepinephrine in both preventing and treatment of hemodynamic changes caused after spinal anesthesia in elective cesarean section. Another objective was to evaluate the effect of these agents on neonate.

Materials and Methods: Our study consisted of 45 patients which were divided into three groups by random. In each group after basic monitoring and spinal anesthesia was performed, 5 mg of ephedrine, 5 micrograms of norepinephrine and 40 micrograms of phenylephrine were administered respectively. During the operation any possible changes in mean arterial blood pressure (MAP) and heart rate were recorded. Perioperative complications of both neonate and mother were controlled and recorded.

Results: The MAP was higher in the norepinephrine group than the phenylephrine and ephedrine groups. The rate of blood pressure in both norepinephrine and phenylephrine groups was higher in comparison with ephedrine group (P = 0.001). MAP was slightly higher in norepinephrine group compared with phenylephrine group. However, in some point of time measuring this difference was significant. Maternal bradycardia was more common in the phenylephrine group with significant difference. (P = 0.003). No cases of vomiting were reported in any of the studied groups. Nausea was more common in ephedrine and phenylephrine groups without significant difference (P = 0.146). The rate of fetal metabolic acidosis in the ephedrine group was significantly higher compared with the other two groups (P = 0.043).

Conclusion: Post-spinal hypotension in parturient undergoing cesarean delivery could be prevented successfully by prophylactic bolus doses of phenylephrine and norepinephrine which causes the least amount of drawbacks and fetal well-being in comparison with ephedrine.

Keywords: Phenylephrine, Ephedrine, Norepinephrine, Spinal Anesthesia, Elective Cesarean Section, Hypotension.

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INTRODUCTION

Based on the updated guidelines for obstetric anesthesia to have a more safe elective cesarean delivery, it is recommended to use neuraxial block whenever feasible (1). The most prevalent side effect caused by spinal anesthesia in obstetrics is Hypotension with a varied incidence rate of 1.9% and 71%. (2). During the pregnancy the sensitivity of nerve fibers to local anesthetics will increase which could cause a rapid onset of sympatholysis that is known to be the most significant causes of hypotension (4).

Adverse maternal outcomes such as dizziness, vomiting, and nausea are all due to Hypotension (5). Decrement of systolic blood pressure disrupts uterine blood flow and fetal circulation, and consequently fetal hypoxia and acidosis. Decrease in systolic blood pressure can compromise uterine

blood flow and fetal circulation, and thus cause intrauterine hypoxia and acidosis. Moreover, hypotension causes prenatal hypoxia-ischemia (HI) and reperfusion injury (7). Neurobehavioral outcome of the newborn could be affected by prolonged high blood pressure (6).

Finding an effective treatment for spinal anesthesia-induced hypotension (SAIH) is one of the main challenges in obstetric anesthesia. Many interventions have examined the usage of crystalloid and colloids before and during anesthesia, but unfortunately didn't reported satisfactory efficiency (9). However, it has been proved that administration of vasopressors is effective in management of SAIH (10, 11). Three of the most prevalent vasopressors that are used to manage spinal hypotension are norepinephrine, phenylephrine, and ephedrine (6, 7). Ephedrine is a well-known and long established drug which is prescribed and used by most anesthetists for treatment and prophylaxis against SAIH. Ephedrine is a adrenergic drug which acts directly as alpha and beta adrenergic agonist. Moreover, ephedrine acts indirectly by releasing norepinephrine from sympathetic neurons. Nowadays, administration of ephedrine causes some concerns because of the possibility of fetal acidosis and supraventricular tachycardia (SVT) (12, 14). Ephedrine has some disadvantages such as slow onset and relatively its long duration which may disturbs the process of titration of blood pressure (10).

Phenylephrine is without beta adrenergic receptor activity, while it is a pure alpha adrenergic receptor agonist which could potently prevent or treat SAIH. Despite the role of phenylephrine in causing bradycardia and reduction of utero-placental perfusion, recent studies have revealed that phenylephrine is capable of improving neonatal outcome by maintaining organ-specific perfusion pressure and mean arterial blood pressure (2).

Norepinephrine has both alpha adrenergic receptor agonistic and weak beta adrenergic receptor agonistic properties. Dissimilar to phenylephrine, norepinephrine has eligible effects on cardiac output and maternal heart rate. In this regard, norepinephrine is introduced to be an effective alternative with better remedial outcomes compared to phenylephrine in obstetric anesthesia purposes (13).

The present study was designed aimed to assess and compare the effectiveness and safety of bolus doses of phenylephrine, ephedrine, and norepinephrine in preventing hemodynamic changes associated with spinal anesthesia in planned cesarean delivery.

Materials and Methods

This study is a randomized prospective clinical trial which was performed after being approved by ethics and research committee of Iran University of medical sciences. At the time interval of October 2019 to September 2021. All parturients were informed about the study and a written consent was obtained from them. We studied 45 patients aged 18-40 years, ASA class I, gestational age 37 weeks and more, singleton pregnancy, height more than 150 cm and weight between 60 to 80 kg, scheduled for elective cesarean section under spinal anesthesia block.

Exclusion criteria include: failure of spinal block, contraindication to spinal block, gestational age less than 36 weeks, height less than 150 cm, drug addiction, patient refusal to participate, underlying diseases including cardiovascular disease, hypertension, diabetes, eclampsia, preeclampsia and any known fetal anomalies.

Sample size calculation

Based on the primary outcomes of mean arterial blood pressure and also previous clinical studies (24), it was assumed that the difference in mean arterial blood pressure and SDs would be 10%. By setting statistical significance level at 5% and the power at 80%, and applying the following formula, it was calculated that the appropriate group size would require 15 patients.

$$\frac{(Z\left(1-\frac{\alpha}{2}\right)+Z(1-\beta)^2(sd1^2+sd2^2)}{d^2}$$

Procedure

A permuted block randomization technique was used in which randomization was conducted right before the patient admission. 15 blocks each with three sections were created. In each of them different method of treatment was included. Each one of them were put in a sealed non transparent envelope and in a specific vase. Each time an envelope was selected randomly and registered in a predetermined table. It continued until all 15 blocks were selected and sample sequence was determined.

On arrival to operating room and after a written consent paper was abstained from parturient,

Medical monitoring was done using pulse oximetry, non-invasive arterial blood pressure, and electrocardiogram for all women participated in our study.

Infusion of ringers solution (5cc/kg) was using Two 20 Gauge IV Cannula were inserted during which basic vital signs were recorded. After that, patients were placed in a sitting position with forward head posture (FHP) and the relaxed shoulders. Preparation of skin was done using povidone-iodine. Then a 25G spinal needle was inserted at the L3-L4 interspace. Subarachnoid (spinal) block chosen for injection of 0.5% hyperbaric bupivacaine based on the the height of patients, 8mg (up to 160cm), 9 mg (height between 160 to 170 cm), and 10 mg (for height above 170 cm) at a rate of 0.2 cc per second were injected. Right before placing the patient in the supine position, (5 µg) of norepinephrine, (40 µg) of phenylephrine and 5 mg of ephedrine were administered.

The patients were positioned supine and an oxygen mask with a flow rate of 5 L / min was given. The patient's vital signs

were assessed using a NIBP device before spinal anesthesia and every minute until the birth and then every 5 minutes until skin closure. The incidence of hypotension and bradycardia were recorded and compared in three groups at each point of time. Nausea and vomiting were also recorded and compared in three groups at each point of time, and in case of occurrence, treatment with 0.4 mg intravenous atropine was considered. In this study, bradycardia was defined as a decrease in heart rate by 30% of baseline or less than 60 beats per minute. If it occurred, the patient was treated with 0.01mg / kg intravenous atropine and repeated up to three times until a response was obtained.

When blood pressure drops to about 30% of baseline blood pressure, in other word when blood pressure decreases to the range of 90 to 60 mm Hg, we call it Hypotension. If it occurred in each group, the same prophylactic dose of the drug administered and repeated, if necessary, until a response was obtained.

After delivery, 50u oxytocin as 10 bolus dose and 40 u IV infusion was slowly administered. Than the patients were sedated with 1 mg of intravenous midazolam. 1500cc-2000cc ringer's lactate and normal saline solutions, based on fluid chart, were given throughout the surgery. After delivery, the cord blood sample was taken for arterial blood gas analysis. Finally, mothers were transported to the recovery room while being monitored with routine equipment.

Data Analysis

Classified data were analyzed based on chi-square analysis and their information was presented as frequency. In the beginning, Kolmogorov-Smirnov normality test was used to check normal distribution of the data. Score of variables were measured by T-test if they followed the normal distribution. If they did not have a normal distribution, the Mann-Whitney test was used. Pearson or Spearman correlation test was applied to examine the correlation between the data. For comparing qualitative variables, Fisher's exact test or Chi-square test were used. SPSS statistics software version: 23.0, was used to analyze the data. P-value ≤ 0.05 was considered as statistically significant.

Ethical Consideration

The study was approved by the ethics committee of Iran University of Medical Sciences with code IR.IUMS.FMD.REC.1399.475.

Results

75 out of 120 eligible patients for spinal block anesthesia in our study were excluded, 69 of whom did not meet the inclusion criteria and 6 refused to participate in the study. Finally, 45 pregnant women were enrolled in our study who randomly divided into three groups. As could be seen from table (1) the differences between the two studied group was not significant based on demographic data such as the operative time.

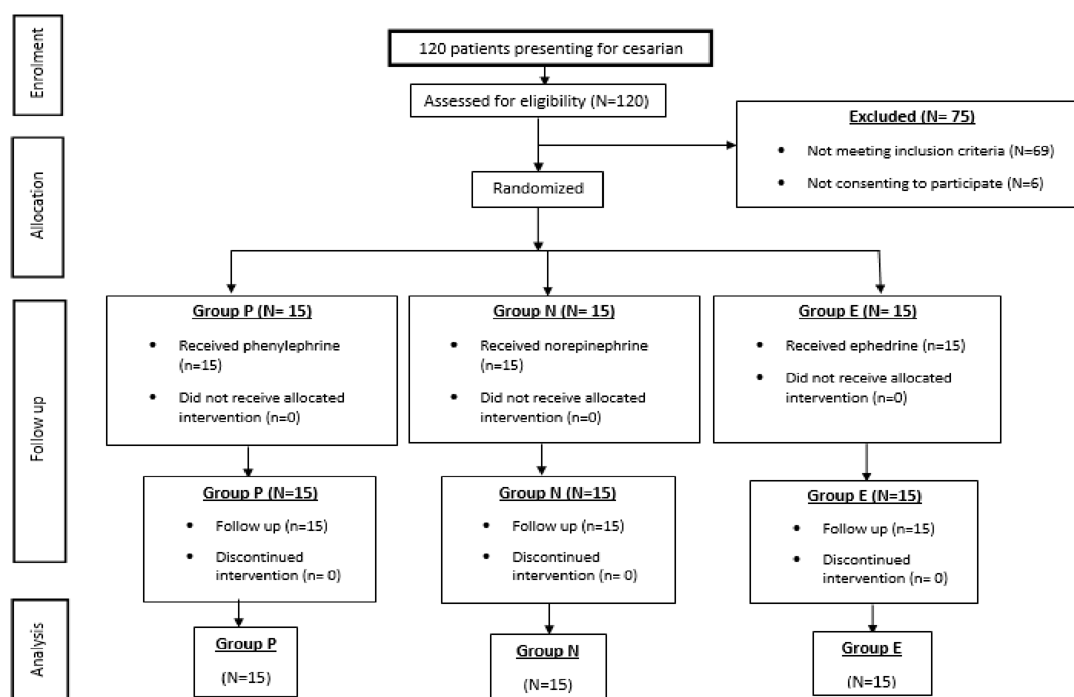

Figure 1: Flow diagram of the study

Table 1: Comparing the data of two studied groups based on their demographic information

	Group E (n=15)	Group P (n=15)	Group N (n=15)	One way ANOVA
	±Mean SD	±Mean SD	±Mean SD	P-value
BMI (Kg/m2)	31.07 ± 3.79	28.02 ± 2.31	28.07 ± 2.58	0.061
Age (year)	28.04 ± 5.35	27.64 ± 4.00	27.40 ± 3.71	0.875
Weight (kg)	81.52 ± 8.91	77.16 ± 6.39	77.36 ± 6.92	0.074
The operative time (min)	43.2 ± 5.18	46.40 ± 4.9	43.8 ± 6	0.089

P-value ≤ 0.05 considered as a statistical significant level.
Norepinephrine: N; Phenylephrine: P; Ephedrine: E; Body mass index: BMI

The differences between the three studied groups based on average basal blood pressure was not significant (p-value=0.469). However, norepinephrine group significantly controlled MAP and prevented its decline compared to the phenylephrine and ephedrine groups. This difference was observed from two minutes after drug administration until the end of surgery. The rate of MAP in participants of group P was slightly lower. However, in some point of time measuring this difference was with frequent significance (table 2).

Table 2: Comparing the studied groups based on average pregnant woman's blood pressure (mmHg)

	Group E	Group N	Group P	One-way ANOVA	
	Mean±SD	Mean±SD	Mean±SD	F	P-value
Basic MAP	89.47±4.7	91.36±5.26	91.49±4.99	0.771	0.469
SA & drug adm	91.38±4.76	92.51±4.59	92.67±4.73	0.337	0.716
1 min	91.98±4.39	93.56±3.98	91.76±5.65	0.646	0.529
2 min	87.31±7.75	94.16±4.05	90.78±5.19	5.102	0.01
3 min	86.49±9.67	94.76±4.13	89.36±4.79	5.939	0.005
4 min	84.58±11.35	95.29±4.02	88.33±3.73	8.365	0.001
5 min	82.84±10.45	96.16±4.03	88.69±3.43	14.6	0.001
6 min	82.51±8.4	95.64±4.11	89.47±3	20.16	0.001
Birth	82.8±6.88	96.29±3.96	90.49±2.47	29.82	0.001
10 min	83.49±3.8	95.78±4.22	91.42±2.34	46.32	0.001
15 min	84.31±2.28	95.51±3.47	92.36±2.59	62.71	0.001
20 min	83.96±2.4	94.98±4.02	92.76±3.33	46.34	0.001
25 min	85.33±3.98	94.44±3.41	93.11±3.78	26.07	0.001
30 min	86±2.77	95.22±3.38	92.98±3.06	36.65	0.001
35 min	84.4±3.34	94.31±3.35	93.16±3.74	36.27	0.001
40 min	85.4±2.23	94.16±3.06	93.27±3.5	39.34	0.001
45 min	85.71±3.57	93.73±2.89	93.89±2.95	33.06	0.001
50 min	85.67±2.39	93.47±3.29	92.76±3.35	30.16	0.001
55 min	85.07±4.23	93.47±2.71	93.33±3.33	28.66	0.001
60 min	86.2±1.55	93.11±3.3	93.62±2.71	37.44	0.001
P-value ≤ 0.05 considered as a statistical significant level. Norepinephrine: N; Phenylephrine: P; Ephedrine: E; Body mass index: BMI					

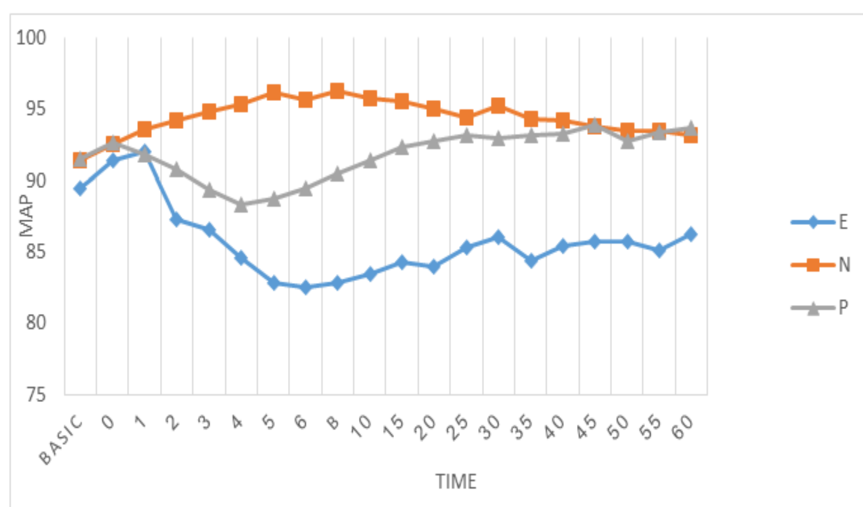

Figure 2: Comparison of mean arterial pressure (MAP) between groups over time

The differences between studied groups based on baseline values of maternal heart rate was not statistically significant (p value= 0.411). Maternal heart rate in ephedrine group increased significantly (p-value= 0.001). Phenylephrine had the most effect on maternal heart rate where it caused 5 cases of bradycardia and subsequent atropine administration. Meanwhile, norepinephrine had steadier effect on maternal heart rate than the other two groups (table 3).

Table 3: Comparing the studied groups based on maternal heart rate (bpm)

	Group E	Group N	Group P	One-way ANOVA	
	Mean±SD	Mean±SD	Mean±SD	F	P-value
Basic HR	75.53±5.78	78.826±6.78	77.93±5.36	0.909	0.411
SA & drug adm	79.87±6.2	80.40±7.05	78.87±5.45	0.226	0.798
1 min	94.27±10.57	84.87±5.69	75.47±5.93	22.17	0.001
2 min	97.67±5.77	85.27±5.6	72.6±7.59	57.88	0.001
3 min	95.67±5.47	85.27±5.06	70.33±8.84	54.58	0.001
4 min	94±6.81	85.67±5.14	69.47±8.96	45.75	0.001
5 min	92.27±5.6	84.87±4.58	71.4±6.49	53.33	0.001
6 min	92.53±6.42	85.13±5.82	71.93±2.71	59.43	0.001
Birth	90.27±7.39	85.13±7.41	74±3.34	25.8	0.001
10 min	89.13±4.91	84.27±8.4	77.2±4.36	14.24	0.001
15 min	86.4±5.44	85.8±4.69	78.13±5.28	12.04	0.001
20 min	86.47±5.88	84.87±4.93	79.47±5.93	6.444	0.003
25 min	85±7.14	85.33±5.05	78.8±6.33	5.227	0.009
30 min	85.6±7.56	85.73±4.48	80.13±6.15	3.995	0.025
35 min	84.93±6.01	85.8±3.8	80.73±7.05	3.299	0.046
40 min	86.07±5.85	85.67±3.22	80.73±6.16	4.812	0.013
45 min	84.53±7.58	84.47±3.52	81.07±5.11	1.845	0.171
50 min	84.47±6.89	84.47±3.83	80.53±5.71	2.452	0.098
55 min	85.33±5.08	85.07±4.86	80.2±6.27	4.234	0.021
60 min	83.8±4.06	84±4.57	80.4±5.93	2.543	0.090
P-value < 0.05 considered as a statistical significant level. Norepinephrine: N; Phenylephrine: P; Ephedrine: E; Heart rate: HR					

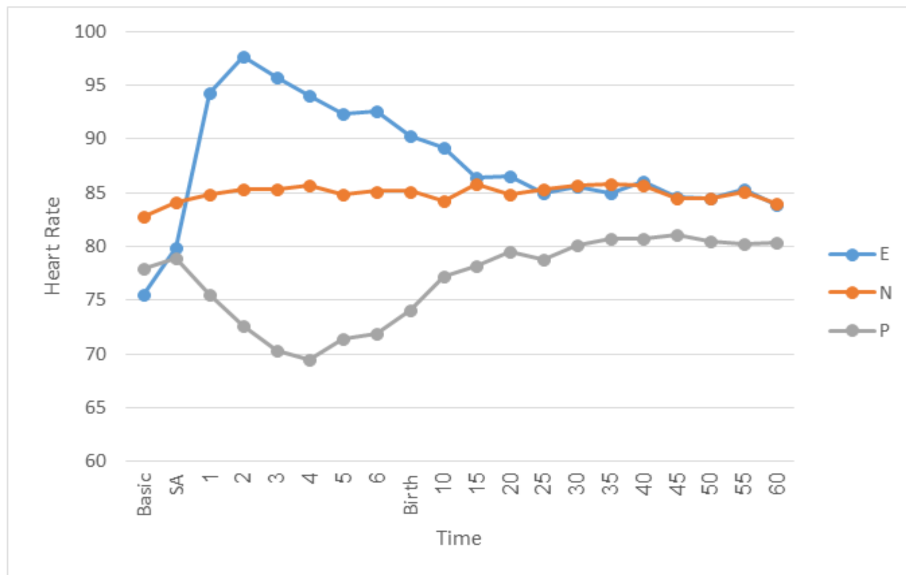

Figure 3: Comparison of heart rate (HR) between groups over time

Table (4) represents umbilical-cord blood gas analysis. According to the data achieved from One-way ANOVA test, the difference between groups regarding HCO3 and PH was significant (p-values = 0.016, 0.009 respectively). The presence of NMA was reported in two neonates of group E, while no such case was reported in other groups. The level of acidosis in ephedrine group was significantly higher in comparison with the other studied groups (p value = 0.043).

Table 4: Neonatal outcome in studied groups

	Group E	Group N	Group P	One-way ANOVA	
Neonatal outcome	Mean±SD	Mean±SD	Mean±SD	F	P-value
PH	7.34±0.05	7.38±0.02	7.38±0.02	5.23	0.009
PCO2	39.31±6.19	38.47±1.55	38.67±1.23	0.20	0.816
HCO3	22.81±1.66	23.73±1.1	23.4±1.18	4.37	0.016

P-value < 0.05 considered as a statistical significant level. Norepinephrine: N; Phenylephrine: P; Ephedrine: E.

Table 5: Comparison between studied groups as regards Neonatal PH

	Tukey's multiple comparison test	
Groups	**Mean Difference**	**P-value**
N-E	0.033	0.033
P-E	0.038	0.013
P-N	0.004	0.929
P-value < 0.05 considered as a statistical significant level. Norepinephrine: N; Phenylephrine: P; Ephedrine: E.		

As regards of maternal complications, none of the three groups experienced vomiting. Only one case of nausea was observed in the ephedrine group and 3 cases in the phenylephrine group; however, the chi-square analysis test did not show a significant difference (P = 0.1465). The same was reported for the need for Iv atropine between the two groups (P = 0.1465).

Four patients in the ephedrine group needed rescue bolus doses due to hypotension, which showed a significant difference with the other two groups (P = 0.0124). Bradycardia was significantly higher in group P than others (P = 0.003).

Table 6: Maternal complications in studied groups

	N (n= 15)		P (n= 15)		E (n= 15)		Chi square test	
	n	%	n	%	N	%	X-squared	P-value
Vomiting	0	0	0	0	0	0	-	-
Nausea	0	0	3	20	1	6	3.8415	0.1465
No of blouses of vasopressors	0	0	0	0	4	27	8.7805	0.0124
Incidence of Bradycardia	0	0	5	34	0	0	11.25	0.0036
Incidence of hypotension	0	0	0	0	4	27	8.7805	0.0124
Iv atropine (to treat nausea)	0	0	3	20	1	6	3.8415	0.1465

Discussion

Based on the data achieved from the present study it was observed that prophylactic bolus dose of either phenylephrine or norepinephrine are more capable of maintaining MAP in comparison with prophylactic bolus dose of ephedrine. Moreover, it was observed that except for bradycardia in phenylephrine group, no serious or significant maternal complications were observed in the studied groups. In association with neonates, general condition in phenylephrine and norepinephrine groups was better compared to the neonates of ephedrine group who developed mild acidosis.

The main mechanism of post spinal hypotension is the decrement of systemic vascular resistance (SVR). This reduction is mainly because of secondary small-sized arteries vasodilation in company with the widening of blood vessels in a mild degree (14). Consequently it has been recommended to use vasopressors to prevent SAIH. This study was performed for comparing the aforementioned three prevalent vasopressors in obstetric patients to know which one is the bets for preventing hypotension without maternal and fetal adverse effects.

Several studies have conducted a comparative study on the effects of norepinephrine, ephedrine, and phenylephrine at various routs and doses of administration. In fact, there is a common idea about the administration of ephedrine for preventing post spinal hypotension in cesarean section which has been challenged until now to compare it with ephedrine and phenylephrine (15). Although the differences between clinical outcomes of the studied groups based on the Apgar scores was not significant, nearly all the studies concluded that administration of henylephrine yields more acceptable fetal acid base status.

The data from our study revealed that administration of phenylephrine and norepinephrine yield more acceptable results comparing with ephedrine in controlling maternal arterial blood pressure, because ephedrine requires more bolus dose (4 cases) for controlling hypotension than to the two studied groups. That was in agree with the Fan et al (2021) study, who noticed the ephedrine cannot control hypotension in low doses. In addition, ephedrine can cause hypertension and maternal dysrhythmias in high doses (16).

In the study by Ashraf et al. (2021), administration of high-dose ephedrine infusion during surgery resulted in hypertension in two cases and tachycardia in three cases. Furthermore, the ephedrine group required more rescue bolus doses to maintain maternal blood pressure during surgery than the other two groups, which was consistent with the present study (2). The data of our study were in line with those achieved by Xu et al (17) who revealed that norepinephrine was a better choice than ephedrine in controlling maternal mean blood pressure, because the patients who received ephedrine experienced higher rate of hypotension compared to those received norepinephrine.

In this study, in group who received norepinephrine a relatively moderate increase in blood pressure was observed compared to those received phenylephrine. On the other hand, these two groups were not different in terms of their need to bolus rescue doses of vasopressors, which was completely consistent with studies by Vallejo et al. and Ashraf et al. (2, 18). Moreover, heart rate decreased in group P compared with groups E and N. This is due to the fact that phenylephrine is an alpha agonist, which causes a reactive bradycardia due to an increase in blood pressure (baroreceptor reflex). On the other hand, due to beta agonist activity of norepinephrine as an adrenergic alpha agonist, it is neutral and causes less negative effect on heart. Consequently, it is more appropriate in maintaining blood pressure without bradycardia effects in comparison with phenylephrine. Our results were completely consistent with the study of Wang et al. (19) and Theodoraki et al. (20); on the other hand, were contrary to the results obtained in the Vallejo et al. study (18) who found that the incidence of bradycardia was similar between the two groups.

HCO3 and PH were decreased in umbilical cord arterial blood in patients treated with ephedrine. In our study, NMA developed in two babies of the studied patients. Actually, the effect of vasopressors on the uteroplacental circulation is a clear explanation for the mechanism of this complication. The decrement of fetal acid base status due to ephedrine crossing the placenta which simultaneously increases the rate of fetal concentration of lactate, glucose, and catecholamine hormones due to the metabolic processes in the fetus that is resulted from activation of beta-adrenergic receptors in the fetus (1).

As we talked about, the present study suggests using both phenylephrine and norepinephrine rather than ephedrine due to their efficiency in improving fetal acid base status. In fact, norepinephrine has a more favorable effect on phenylephrine. Because of the possibility of decreased cardiac output and bradycardia, norepinephrine affects feta maternal physiology, which causes numerous side effects on placental perfusion (22).

Moreover, ephedrine is able to cross the placenta, while norepinephrine does not have such ability. The results of this study were completely agreed with the studies conducted by Ashraf et al. (2), Xu et al. (17) and Fitzgerald et al. (23). Anyway, it is not in line with the data presented by Fan et al (16) in which the two studied groups of norepinephrine and ephedrine were not significantly different based on arterial blood gas analysis (16).

Nausea and vomiting are two common complications in obstetrics anesthesia. In this study, the incidence of nausea in the phenylephrine and ephedrine groups was found to be higher than the norepinephrine group, which responded well to intravenous atropin. Our findings were in agree with studies by (16) Fan et al., Vallejo et al. (18) and Ashraf et al. (2). Any increase in vagal tone after the reduction of preload, may be the main influencing cause of nausea and vomiting. None of the observed complications were severe.

Conclusion

To sum up, it could be said that the data achieved from the present study revealed that both phenylephrine and norepinephrine has more suitable effects on preventing post spinal hypotension during cesarean section. Moreover, these medications act through maternal hemodynamic stability and fetal outcome with a more desirable remedial outcome of norepinephrine over phenylephrine on maternal heart rate and nausea.

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