Original article

A PROSPECTIVE, RANDOMIZED, DOUBLE-BLIND, COMPARATIVE STUDY OF PHENYLEPHRINE AND EPHEDRINE IN TREATING HYPOTENSION DURING CESAREAN SECTION UNDER SPINAL ANESTHESIA
Vasoconstrictors for Hypotension During cs

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Abstract

Introduction: *Hypotension may affect 70–75% of patients undergoing cesarean section (CS) under spinal anesthesia (SA) and may have detrimental effects on both the mother and the fetus. Our study attempts to compare the effectiveness of phenylephrine and ephedrine in treating SA-induced hypotension in CS and their impact on the fetus.* ***Methods:*** *Forty adult pregnant female patients undergoing elective CS under SA were randomly divided into two groups to receive phenylephrine 100 μg IV bolus and ephedrine 6 mg IV bolus when the systolic blood pressure (SBP) dropped below 20% of the baseline. After delivery of the fetus, the umbilical artery blood sample was taken for blood gas analysis. Apgar score was recorded at 1 and 5 minutes post-delivery.* ***Results:*** *Significant differences were observed in heart rate (HR), SBP, and diastolic blood pressure (DBP), with HR being lower and SBP and DBP being higher in the Phenylephrine group. No significant difference was seen in the Apgar scoring, but uterine artery pH was significantly higher in the Phenylephrine group.* ***Conclusion:*** *Phenylephrine and ephedrine are equally effective in treating SA-induced hypotension in patients undergoing CS. Neonates of patients receiving phenylephrine had significantly higher pH than those receiving ephedrine, although the eventual neonatal outcome, as assessed by Apgar scoring, remained equally good with both drugs.*

Keywords: *Phenylephrine; Ephedrine; Cesarean Section; Spinal Anesthesia; Hypotension; Apgar Score*

Introduction

With the ever-increasing outreach of health care services, Cesarean sections now account for over 21% of the total number of births worldwide[1]. Regional anesthesia is the preferred modality for Cesarean deliveries as it avoids the maternal risks of general anesthesia, such as aspiration of gastric contents and difficulty with airway management. Furthermore, it allows administration of fewer drugs, resulting in a better adverse effect profile and a lower risk of anaphylaxis; ensures an awake mother and an attentive neonate, thereby facilitating early breastfeeding and maternal bonding; allows early mobilization and imparts better postoperative analgesia[2,3]. Spinal anesthesia is the most frequently used regional anesthesia technique for Cesarean deliveries because of its relative ease of administration and better safety profile. But it may be associated with maternal hypotension in 70–75% of the patients[4,5]. Hypotension during spinal anesthesia for Cesarean deliveries may have detrimental effects on both mother and neonate. Attention has been focused in the literature on the methods for preventing hypotension. Measures like intravenous (IV) preloading and uterine displacement decrease hypotension incidence and are routinely used. Hypotension during spinal anesthesia for Cesarean sections remains a common clinical problem despite strict adherence to these measures.

A vasopressor drug is often required to counter these episodes of hypotension swiftly. Various drugs have been used for this purpose, with phenylephrine and ephedrine being the most commonly used. Multiple studies have compared these two agents but have produced contrasting results, with some favoring ephedrine while others phenylephrine[6-9]. This study aims to compare the effectiveness of phenylephrine and ephedrine in

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treating spinal anesthesia-induced hypotension in cesarean section and their effect on the fetus.

Methods

A prospective, randomized, double-blind, comparative study was carried out on forty adult pregnant female patients who developed hypotension while undergoing elective cesarean section under spinal anesthesia at our institution. Ethical approval for conducting the study was obtained from the institutional ethical research committee. A written, informed consent was obtained from all the selected patients. American Society of Anesthesiologists (ASA) grade II female patients with uncomplicated singleton pregnancy and no known fetal abnormality undergoing elective cesarean section at term were included. Patients having pregnancy-induced hypertension, any co-existing systemic disease, hypersensitivity to local anesthetics, local skin infection or spinal deformities, those on anticoagulants or having bleeding disorders, and those who refused to participate in the study were excluded.

The sample size was calculated based on data from the study by Thomas et al. [10], using umbilical artery pH as the primary outcome variable. Assuming the same estimated sample size, 20 patients per group will give a β risk of 90% at an α level of 0.05 for detecting a change of 0.05 units in uterine artery pH. The selected patients were randomly divided into two groups of 20 patients, using computer-generated randomization. Patients in group A received phenylephrine 100 µg IV bolus, and group B received ephedrine 6 mg IV bolus whenever the systolic blood pressure (SBP) dropped below 20% of the baseline.

Pre-anesthetic evaluation, including a detailed history and a thorough physical examination, was done for all patients. Routine hematological and biochemical investigations appropriate for the patients were ordered. The patients were administered tablet ranitidine 150 mg on the night before surgery. On the day of surgery, the patients had been assessed again, nil by mouth status was confirmed, and a written, informed consent was taken. Three readings of non-invasive blood pressure (NIBP) and heart rate (HR) were taken in the preoperative period at 5 minutes intervals. The patients were lying supine with a pillow under their right hip. The mean of these three readings was taken as the baseline value.

One of the researchers allocated the patients to one of the two groups after matching the serial number of the patient with the computer-generated random numbers. Based on the allocated group, the researcher then prepared phenylephrine (100 µg mL^{-1}) or ephedrine (6 mg mL^{-1}) solution and labeled the same with only the patient's name. These syringes were handed over to the other researcher involved in the intraoperative proceedings and subsequent data collection. The first researcher was blind towards the collected data, while the second researcher was blind towards the contents of the syringes.

Inside the operation theatre, routine monitors, including electrocardiography, pulse oximetry, and NIBP, were connected to the patient. Two wide bores (18-gauge) IV lines were secured, and the patient was preloaded with 10 mL Kg^{-1} of Ringer's lactate solution IV over 15 minutes and after that 6 mL kg^{-1} h^{-1} continuous IV infusion. With the patient in the left lateral position, lumbar puncture was performed at the L$_{3-4}$ or L$_{4-5}$ level, through midline approach, using a 26-gauge Quincke's spinal needle. After the dural puncture, 2.4 mL of hyperbaric bupivacaine 0.5% solution was injected intrathecally, and the patient was turned supine with a wedge under the right hip. Oxygen was administered at the rate of 5 L min^{-1} through a face mask. After delivery of the fetus, oxytocin 15 units was administered as slow IV infusion. Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) measurements were noted every two minutes for ten minutes post administration of spinal anesthesia and every five minutes after that, till the end of the surgery. Whenever the SBP fell below 20% of the baseline value, 1 mL of the study drug was administered IV bolus. The upper target level of sensory block was T5, and it was assessed by loss of pinprick discrimination at 5 minutes and then further at 15 minutes post administration of spinal anesthesia. Surgery was started once the target sensory block level was achieved.

Immediately after delivery of the fetus, the umbilical cord was clamped, and a blood sample from the umbilical artery was taken for blood gas analysis. 1 mL of blood sample was heparinized with 0.1 mL of heparin (1000 IU mL^{-1}), and blood

gas analysis was performed within 5 minutes of clamping the cord. Apgar score was noted at 1 and 5 minutes post-delivery of the fetus. The total surgical time and the time of uterine incision, and the delivery of fetus was noted. The time of administration of the study drug and the total number of boluses infused were recorded.

The collected data are presented using mean (with standard deviation) for quantitative variables, and categorical variables are presented in frequencies along with respective percentages. The statistical comparison for quantitative variables is done using Student's t-test for two independent groups. For categorical variables, the Chi-square test is used according to the nature of the data. Data are entered and coded in MS Excel (Version, 2019), and all statistical analyses are performed using SPSS software (Version 20, SPSS Inc, Chicago, IL, USA). P-value less than 0.05 is considered statistically significant.

Results

There was no statistically significant difference between the groups regarding background variables rendering the two groups comparable (Table 1). Statistically significant differences in HR were observed between the groups at 6th, 8th, 10th, 15th, and 20th-minute intervals, with HR being lower in Group A (Figure 1). Statistically significant differences were again observed in SBP and DBP at 25th, 40th, 45th, 50th, 55th, 60th, 65th and 70th, and 6th, 25th, 40th, 45th, 50th, 55th, 60th, 65th, and 70th-minute intervals, respectively, with both SBP and DBP being higher in Group A (Figure 2). No statistically significant difference was found in the time of administration of the first vasopressor bolus, but the total number of vasopressor boluses administered was significantly higher in Group A (Table 2). Apgar scores in the two groups were comparable, but the uterine artery pH was significantly higher in Group A (Table 3). Adverse effects

Table 1: Comparison of baseline quantitative and qualitative variables between the groups. Data are presented as mean (standard deviation (SD)) and number (percentage (%)). *P-value < 0.05

Quantitative Variable	Group A	Group B	P-value
Age (years)	25.95 (3.49)	25.85 (4.08)	0.38
Weight (kg)	69.60 (6.71)	68.70 (6.74)	0.78
Height (cm)	162.95 (4.58)	163.50 (5.41)	0.09
Gestational Age (weeks)	38.55 (1.39)	38.45 (0.94)	0.31
Baseline HR (bpm)	88.54 (13.25)	92.36 (11.68)	0.34
Baseline SBP (mmHg)	122.50 (9.13)	120.8 (13.59)	0.66
Baseline DBP (mmHg)	82.8 (7.5)	81.05 (11.52)	0.57
Spinal anesthesia to delivery Time (minute)	15.24 (6.76)	14.48 (2.29)	0.73
Uterine incision to delivery Time (second)	91.80 (14.86)	94.20 (13.13)	0.59
Duration of surgery (minute)	74.40 (8.29)	72.65 (8.25)	0.83
Parity (number (%)):			
1	14 (70%)	10 (50%)	
2	5 (25%)	9 (45%)	
3	1(5%)	1(5%)	0.40

HR – heart rate; bpm – beats per minute; MAP – mean arterial pressure; ASA – American Society of Anesthesiologists
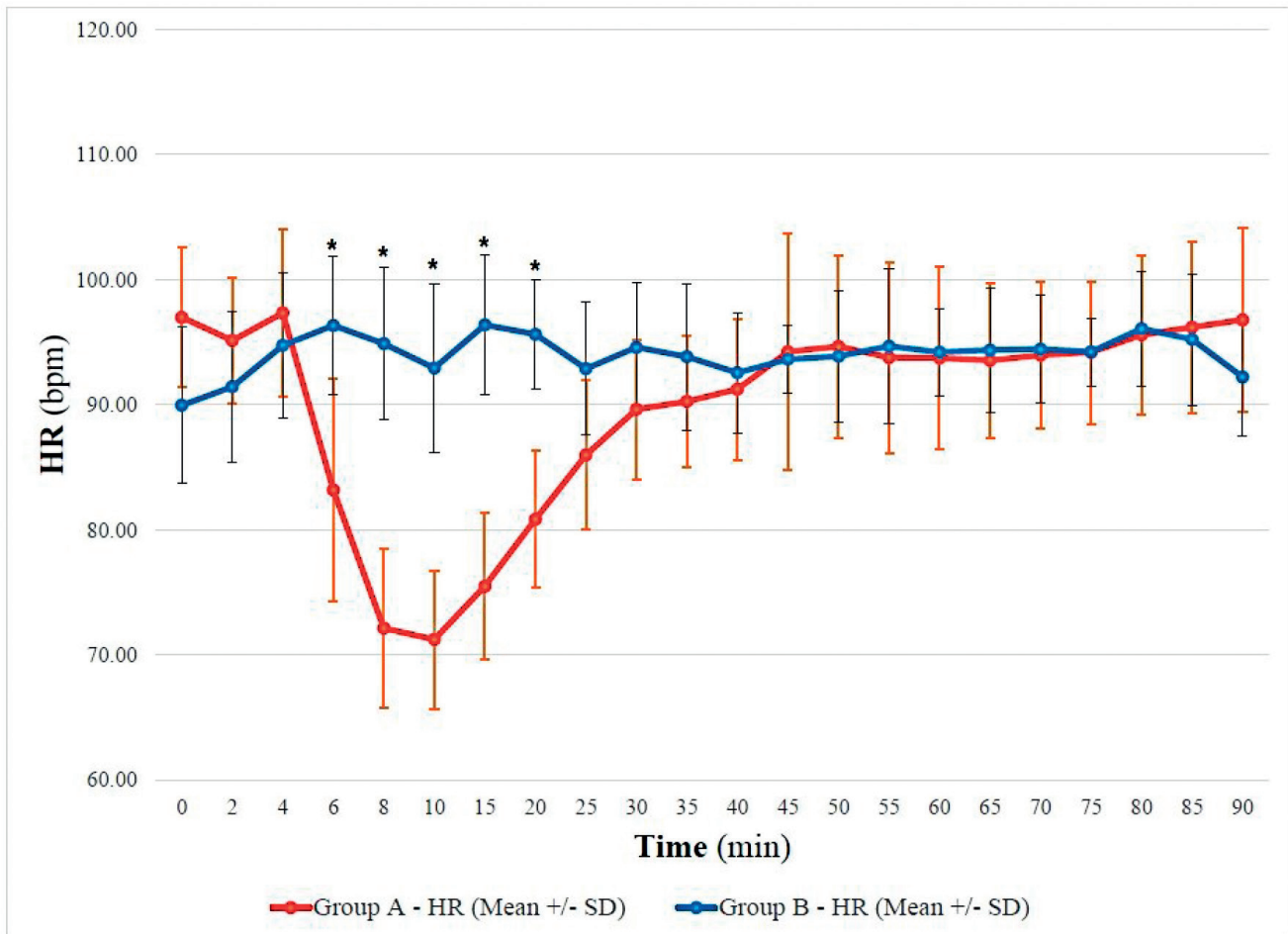
Figure 1: Comparison of heart rate (HR) between the groups presented as mean (standard deviation (SD)). *P-value < 0.05; bpm – beats per minute;

Table 2: Time of administration of first vasopressor bolus, total number of vasopressor boluses required, and the incidence of intraoperative nausea. Data are presented as mean (standard deviation (SD)) and number (percentage (%)). *P-value < 0.05

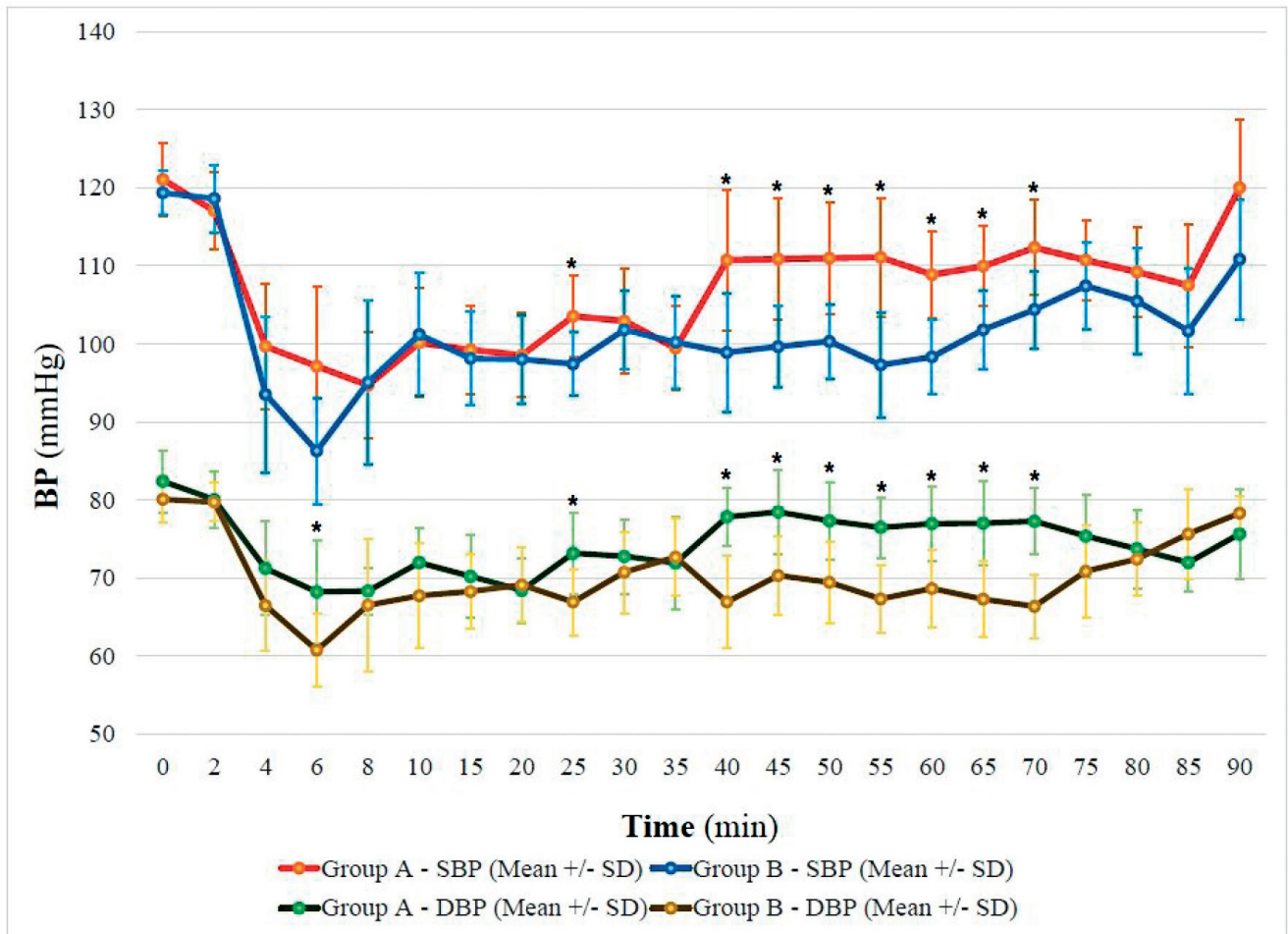| Variable	Group A	Group B	P value
Time of administration of first vasopressor bolus (min)	4.60 (1.31)	5.60 (2.01)	0.07
Total number of vasopressor boluses administered	3.85 (0.93)	1.50 (0.61)	< 0.01*
Nausea (N (%))	3 (15%)	4 (20)	0.68

Figure 2: Comparison of systolic (SBP) and diastolic (DBP) blood pressure (BP) as mean (standard deviation (SD)). *P-value < 0.05, (BP – blood pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure;)

Table 3: Apgar score and uterine artery pH. Data are presented as mean (standard deviation (SD)). *P-value < 0.05

Variable	Group A	Group B	P value
Apgar score	8.65 (0.49)	8.55 (0.51)	0.53
Uterine artery pH	7.34 (0.04)	7.31 (0.05)	0.04*

like vomiting and bradycardia were not observed in any of the patients, but 15% of patients in Group A and 20% of patients in Group B complained of nausea during the intraoperative period (Table 2). The difference in the incidence of nausea between the groups was statistically insignificant.

Discussion

In the current study, we compared phenylephrine and ephedrine regarding their efficacy in treating the hypotension, their effect on the fetus, and their adverse effect profile. Both of these agents effectively treated spinal anesthesia-induced hypotension, although both the SBP and the DBP were significantly higher in the phenylephrine group. The total number of boluses required for preventing hypotension was also significantly higher in the phenylephrine group, indicating that though phenylephrine caused a steeper rise in BP, its effect was short-lived compared to ephedrine. None of the patients in either group developed bradycardia, but the HR in the phenylephrine group was significantly lower than the ephedrine group. The incidence of nausea and vomiting was comparable between the two groups. 15% of patients developed nausea in the phenylephrine group, and 20 %

in the ephedrine group. None of the patients complained of vomiting. No significant difference was observed in the Apgar scores (at 1 and 5 minutes) between the groups, with the scores remaining more than eight in all the neonates. A statistically significant difference was observed in the umbilical artery pH, with phenylephrine causing less fetal acidosis than ephedrine.

Hypotension during spinal anesthesia for Cesarean delivery is a commonly encountered complication. It can have detrimental effects on both the mother and the fetus. In the mother, it causes symptoms of low cardiac output, such as nausea, vomiting, and dizziness. Hypotension also decreases the uteroplacental blood flow, resulting in impaired fetal oxygenation and fetal acidemia. Vasopressors are often required to counter this hypotension. The two most commonly used vasopressors for this purpose are ephedrine and phenylephrine. Ephedrine effectively increases arterial pressure, predominantly through a β receptor-mediated increase in cardiac output, with relative preservation of uteroplacental blood flow. Phenylephrine, an α agonist, was believed to decrease uteroplacental blood flow based on various animal studies[11-13]. Trials have contradicted this assumption and concluded that phenylephrine selectively spares the uteroplacental blood flow, and the elevation of systolic arterial pressure by phenylephrine is significantly higher than other vasopressors[14,15].

A similar study was conducted by Thomas et al.[10] in which 38 healthy women undergoing elective Cesarean section under spinal anesthesia at term were randomly allocated to receive boluses of either phenylephrine 100 μg or ephedrine 5 mg to treat hypotension. They reported comparable maternal SBP and cardiac output changes in both groups, but lower mean maternal HR and higher mean umbilical artery pH in the phenylephrine group. Prakash et al.[6] compared maternal hemodynamic changes and neonatal well-being following bolus administration of 6 mg ephedrine and 100 μg phenylephrine to counter hypotension in 60 term parturients undergoing elective cesarean delivery under spinal anesthesia. They reported that both drugs were equally effective in the treatment of hypotension. The patients in the phenylephrine group had significantly lower heart rates than patients in the ephedrine group. No difference was observed in the adverse effect profile between the

two groups. The neonates of women treated with phenylephrine had higher umbilical cord pH and base deficit values. Apgar scores at 1, 5, and 10 min, and neurobehavioral scores after two hours, four hours, 24 hours, and 48 hours after birth were similar between the groups. The results of both of these studies are consistent with our research. The difference in umbilical arterial pH values may be attributed to the fact that ephedrine crosses the placenta. Therefore, ephedrine may increase the fetal metabolic rate by β adrenergic stimulation leading to fetal acidosis[16,17].

Abdalla et al.[7] conducted a study on forty preeclamptic patients undergoing elective cesarean section under spinal anesthesia. They were randomly divided into two groups and were administered 100 μg phenylephrine and 6 mg ephedrine respectively to develop hypotension. A statistically significant difference was observed in SBP, DBP, and HR between the two groups, with SBP and DBP being higher and HR being lower in the phenylephrine group. No significant difference was observed in the Apgar scores and umbilical artery pH between the groups. Mohta et al.[8] conducted a similar study on eighty preeclamptic women using phenylephrine 50 μg or ephedrine 4 mg boluses. Blood pressure changes following vasopressor administration were similar in both groups, but heart rate remained higher after ephedrine at all time points. The primary outcome measure of umbilical artery pH and adverse effect profiles were comparable.

The results of both studies agree with our research except the result on umbilical artery pH. This lack of difference in the umbilical artery pH could be attributed to preeclampsia. Preeclamptic patients report a lower incidence of hypotension under spinal anesthesia leading to relatively higher umbilical artery pH[9]. Lee et al.[18] conducted a systematic review of various randomized controlled trials comparing phenylephrine with ephedrine in treating spinal anesthesia-induced hypotension patients undergoing cesarean section. They concluded that there was no difference between phenylephrine and ephedrine in their efficacy for managing hypotension. They further stated that the neonates of mothers receiving phenylephrine had higher umbilical artery pH, although the risk of severe fetal acidosis (umbilical artery pH < 7.20) was similar in both groups.

Conclusion

The current study demonstrates that both phenylephrine and ephedrine are equally effective in treating spinal anesthesia-induced hypotension during cesarean section and have a similar adverse effect profile. Neonates of patients receiving phenylephrine had significantly higher pH than those receiving ephedrine, although the eventual neonatal outcome, as assessed by Apgar scoring, remained equally good with both drugs.

References

1.Boerma T, Ronsmans C, Melesse D, Barros AJD, Barros F, Juan L, et al. Global epidemiology of use of and disparities in cesarean sections. The Lancet. 2018; 392(10155):1341–48.

2.Dagli R, SongurDagli S. Anaesthetic Method Preference of Obstetricians for Cesarean Section. Turkish Journal of Anesthesia and Reanimation. 2015; 43(1):41–46.

3.Allman KG, Wilson IH. Oxford Handbook of Anesthesia. 4th ed. Oxford University Press; 2016:737–46.

4.Šklebar I, Bujas T, Habek D. Spinal Anesthesia-induced Hypotension in Obstetrics: Prevention and Therapy. Acta Clin Croat. 2019;58(1):90–95.

5.Butwick A, Columb M, Carvalho B. Preventing spinal hypotension during Cesarean delivery: what is the latest? Br J Anaesth. 2015; 114(2):183–86.

6.Prakash S, Pramanik V, Chellani H, Salhan S, Gogia A. Maternal and neonatal effects of bolus administration of ephedrine and phenylephrine during spinal anesthesia for cesarean delivery: a randomised study. Int J ObstetAnesth. 2010; 19(1):24–30.

7.Abdalla E, Wahaba O, Mohammed M, Almaz M. Ephedrine versus phenylephrine effects on fetal outcome and hemodynamics of preeclamptic mothers undergoing cesarean section under spinal anesthesia. Ain-Shams Journal of Anaesthesiology. 2014; 7(2):215–20.

8.Mohta M, Duggal S, Chilkoti G. Randomised double-blind comparison of bolus phenylephrine or ephedrine for treatment of hypotension in women with pre-eclampsia undergoing cesarean section. Anesthesia. 2018; 73(7):839–46.

9.Cooper DW, Sharma S, Orakkan P, Gurung S. Retrospective study of association between choice of vasopressor given during spinal anesthesia for high-risk cesarean delivery and fetal pH. Int J ObstetAnesth 2010; 19:44–49.

10.Thomas DG, Robson SC, Redfern N, Hughes D, Boys RJ. Randomized trial of bolus phenylephrine or ephedrine for maintenance of arterial pressure during spinal anesthesia for cesarean section. British Journal of Anesthesia 1996; 76:61–65.

11.Erkinaro T, Makikallio K, Acharya G, Pakkila M, Kavasmaa T, Huhta JC, et al. Divergent effects of ephedrine and phenylephrine on cardiovascular hemodynamics of near-term fetal sheep exposed to hypoxemia and maternal hypotension. Acta Anaesthesiol Scand. 2007; 51(7):922–28.

12.Kim YH, Veille JC, Cho MK, Kang MS, Kim CH, Song TB, et al. Chronic hypoxia alters vasoconstrictive responses of femoral artery in the fetal sheep. J Korean Med Sci. 2005; 20(1):13–19.

13.Erkinaro T, Kavasmaa T, Pakkila M, Acharya G, Makikallio K, Alahuhta S, et al. ephedrine and phenylephrine for the treatment of maternal hypotension in a chronic sheep model of increased placental vascular resistance. Br J Anaesth. 2006; 96(2):231–37.

14.Ngan Kee WD, Tam YH, Khaw KS, Ng FF, Critchley LA, Karmakar MK, et al. Closed-loop feedback computer controlled infusion of phenylephrine for maintaining blood pressure during spinal anesthesia for Cesarean section: a preliminary descriptive study. Anesthesia 2007; 62(12):1251–56.

15.Macarthur A, Riley ET. Obstetric anesthesia controversies: vasopressor choice for postspinal hypotension during Cesarean delivery. Int Anesthesiol Clin. 2007; 45(1):115–32.

16.Ngan Kee WD, Khaw KS, Tan PE, Ng FF, Karmakar MK. Placental transfer and fetal metabolic effects of phenylephrine and ephedrine during spinal anesthesia for cesarean delivery. Anesthesiol. 2009; 111(3):506–12.

17.Lee A, Kee WD, Gin T. A quantitative, systematic review of randomized controlled trials of ephedrine versus phenylephrine for the management of hypotension during spinal anesthesia for cesarean delivery. AnesthAnalg. 2002; 94(4):920–6.

18.Lee A, Ngan Kee W, Gin T. A Quantitative, Systematic Review of Randomized Controlled Trials of Ephedrine Versus Phenylephrine for the Management of Hypotension During Spinal Anesthesia for Cesarean Delivery. Anesthesia& Analgesia. 2002; 94(4):920–26.