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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Comparison of efficacy and safety of preemptive infusion protocols of ephedrine and phenylephrine – prevention of hypotension and effects on hemodynamic parameters during spinal anesthesia for caesarean section

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SUMMARY
Introduction/Objective Spinal anesthesia (SA) for cesarean section may lead to significant changes in hemodynamic parameters, especially hypotension.
The aim of this study was to determine and compare the efficacy and safety of preemptive infusion protocols of the two most commonly used vasopressors, ephedrine (Group E, n = 29) and phenylephrine (Group P, n = 31) not only on prevention of hypotension but also to determine their effect on hemodynamic parameters, such as stroke volume (SV) and cardiac output (CO) using a continuous non-invasive hemodynamic monitor.
Methods The infusion of ephedrine was administered at the rate of 5 mg/min. immediately after SA. Phenylephrine was administered at an infusion rate of 25 μg/min for two minutes prior to SA.
Results In Group E, mean systolic blood pressure (SBP) and heart rate (HR) were similar to baseline. CO was higher ($p < 0.001$), while systemic vascular resistance (SVR) was lower than baseline ($p < 0.001$). In Group P, mean SBP and diastolic blood pressure (DBP) were lower than baseline, respectively ($p = 0.006$, $p < 0.001$). SBP, DBP, CO, SV, SVR, and HR were significantly different between the E and P groups ($p < 0.001$).
Conclusion E and P vasopressors are both effective in the prevention of hypotension during SA.
Keywords: cesarean section; spinal anesthesia; ephedrine; phenylephrine; hypotension; hemodynamic parameters

INTRODUCTION

Due to the significantly higher percentage of morbidity and mortality under general anesthesia, spinal anesthesia (SA) is now the method of choice [1]. Cesarean section under SA leads to significant changes in hemodynamic parameters, such as preload, stroke volume (SV), cardiac output (CO), heart rate (HR) and systemic vascular resistance (SVR) [2]. Hypotension occurs within approximately 70–80% of cases as a consequence of sympathetic blockade in the affected areas of anesthesia, which might cause organ and placental hypoperfusion. Acute hypotension reduces cerebral perfusion, which leads to transient ischemia and activates the vomiting center [3–6]. Fall in CO reduces oxygen delivery to organs and tissues, results in buildup of oxygen debt, causing complications after SA [7, 8, 9]. Other side effects of hypotension during SA are nausea, vomiting, dizziness, respiratory problems, and fetal acidosis [10, 11].

The most commonly used drugs for hemodynamic optimization during cesarean section are ephedrine and phenylephrine [6, 11, 12]. Ephedrine leads to greater venoconstriction than arteriolar constriction, increases BP, HR, improves venous return (preload), increases CO, and restores uterine perfusion [13]. Ephedrine may cause tachyphylaxis, and is associated with increased risk of fetal acidosis [11, 13]. Phenylephrine increases venoconstriction and arterial constriction, which increases BP, results in venous tone increase and favors venous return (preload) and increases SVR [13–16].

The main goal of this study was to determine and compare the efficacy and safety of preemptive infusion protocols of ephedrine and

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phenylephrine not only on hypotension prevention but also the associated hemodynamic changes during SA for cesarean section. Our hypothesis was that the protocol of application of these drugs is of importance for hemodynamic stability and that application of the given doses of ephedrine and phenylephrine infusion prevents hypotension during the planned caesarean section in SA.

METHODS

This study was designed as prospective and randomized and was approved by the ethics committee of Dr Dragiša Mišović – Dedinje University Hospital Center, Belgrade, Serbia, with the protocol no. 01-5293/23, on April 28, 2017. This study included 60 patients (from June 25, 2017 to April 25, 2018) divided randomly into Group P and Group E. The patients gave written informed consent to participate in the study. Inclusion criteria were as follows: patients aged between 18 and 40, American Society of Anesthesiologists (ASA) 1 or 2 physical status, and single fetus. Exclusion criteria were as follows: less than 36 weeks gestation, presence of cardiac, vascular, or neural diseases, body weight under 50 kg or greater than 100 kg, height under 150 cm, and presence of contraindications for SA.

Protocol P Group

Two minutes before the administration of SA, Group P received 25 μg/min. of phenylephrine infusion and this was continued at 25 μg/min. for the next three minutes. If SBP was unchanged or reduced, the infusion resumed at the same rate. If SBP was greater than 20% below baseline, patients received a rescue bolus of 50 μg phenylephrine intravenously (iv). If bradycardia occurred together with SBP less than 20% below baseline, the infusion of phenylephrine was continued at 25 μg/min., and 0.5 mg atropine was administered iv. If bradycardia occurred with SBP equal to or higher than baseline, phenylephrine infusion was discontinued. If SBP exceeded 20% of the baseline, the infusion of phenylephrine was discontinued.

Protocol E group

Group E patients received ephedrine immediately after SA injection at a dose of 5 mg/min. for the first three minutes. The same dose was continued where SBP was unchanged or lower than the baseline. If SBP decreased more than 20% of baseline, a rescue bolus dose of 5 mg ephedrine was given iv. Where SBP was greater than 20% of the baseline, ephedrine infusion was discontinued. Both infusions were administered via infusion pump Argus 600S (Argus Medical, Heimberg, Switzerland).

Bradycardia was defined as a HR under 60 beats per minute while hypotension was defined as a reduction in SBP greater than 20% of baseline. Hypertension represents increase of SBP greater than 20% above the baseline.

All the patients received 50 mg of ranitidine iv and were preloaded with 500 ml of Hartmann's solution. During the cesarean section the infusion of Hartmann's solution was resumed. BP, HR, electrocardiogram, and oxygen saturation were recorded using the DASH® 4000 monitor (GE Medical Systems Information Technologies Inc., Chicago, IL, USA). BP was measured automatically at three-minute intervals. Pre-induction values of BP, HR, CO, SV, and SVR were recorded with continuous non-invasive hemodynamic monitoring LiDCO Rapid^{V2}CNAP (LiDCO Ltd, London, UK) and the parameters were measured continuously up to the end of the surgical procedure. LIDCO Rapid^{V2}CNAP contains a module for non-invasive continuous monitoring of arterial pressure using a double finger cuff. The Pulse CO^{R} is a pulse pressure algorithm that calculates SV values by the detection of variations in arterial pulse, from the BP waveform using pulse power analysis pressure. It provides a nominal value for SV, CO and SVR using patient demographic data of height, weight, and age. SA was given in the sitting position using a "pencil point" spinal needle of 25G (Pencan® B.Braun, Melsungen, Germany). The patients received bupivacaine-spinal 0.5% 2–2.2 ml in the L3–L4 intervertebral space. The patients were then returned to the previous supine position with the operating table tilted to the left side by 15°.

Umbilical vein blood gas analyses were performed for acidity (pH), partial oxygen pressure (PO_2), partial carbon dioxide pressure (PCO_2), and base excess (BE). Apgar score at the first and fifth minute was recorded for each newborn. The times from spinal injection to baby delivery and from SA until the end of surgery were also recorded.

For statistical analysis we used Kolmogorov–Smirnov test to examine distribution, then parametric Student's t-test for two independent groups' comparison, the Wilcoxon signed-rank test for paired groups, and χ^2 test for frequency distribution analysis, using SPSS Version 19.0 (IBM Corp., Armonk, NY, USA). Before the beginning of the study, we performed the statistical power of study analysis, and our sample size was sufficient at power of 80%; $p < 0.05$ was considered significant.

RESULTS

Demographic characteristics and medical history of the patients are presented in Table 1. The body weight and height were higher in Group E ($p = 0.002$, $p = 0.086$, respectively, Student's t-test, Table 1). Changes in the mean values of hemodynamic parameters between the groups were analyzed before (baseline), and at the time of vasopressor infusion (Table 2).

Mean baseline values of the hemodynamic parameters were not significantly different between the two groups (baseline values, p^{EP}, Table 2). The mean values SBP, DBP, CO, SV, SVR, and HR changed significantly during the ephedrine and phenylephrine infusions ($p^{EP} < 0.001$, Student's t-test, Table 2).

During the infusion, the mean values of SBP, DBP, CO, SV, and HR were significantly higher in the Group E compared to Group P, while the mean SVR was significantly lower in the Group E compared to the Group P (Table 2).

Table 1. Patient characteristics

Charactheristic	Group E (n = 29)	Group P (n = 31)	p
Age (year)	32 (4)	31 (4)	0.335
Weight (kg)	83 (10)	75 (9)	0.002*
Height (cm)	170 (6)	167 (6)	0.086
Gestational age (weeks)	39 (38–40)	39 (38–40)	0.942
Number of previous deliveries	2 (1–3)	2 (1–3)	–
ASA physical status I	18 (62%)	18 (58%)	0.752
ASA physical status II	11 (38%)	13 (42%)	

E – ephedrine; P – phenylephrine; ASA – American Society of Anesthesiologists physical status
*significant p < 0.05, mean (sd), median (min–max. range), n (%), Student's t-test, χ^2 test

During the ephedrine infusion, the mean DBP was significantly lower compared to the baseline values ($p^{12} = 0.005$, Wilcoxon's test, Table 2). Mean values of CO and SV were significantly higher during ephedrine infusion compared to the baseline values ($p^{12} < 0.001$, Wilcoxon's test, Table 2); while SVR was significantly lower ($p^{12} < 0.001$, Wilcoxon's test, Table 2).

In Group P, mean values of CO and SVR were not significantly changed during the infusion compared to the baseline values. During phenylephrine infusion, the mean SBP was lower than baseline ($p^{12} = 0.006$, Wilcoxon's test, Table 2), as was DBP ($p^{12} < 0.001$, Wilcoxon's test, Table 2). SV was significantly increased compared with baseline ($p^{12} = 0.001$, Wilcoxon's test, Table 2). HR was significantly higher in Group E compared to Group P ($p^{EP} < 0.001$, Student's t-test, Table 2), and significantly lower than the baseline in Group P ($p^{12} < 0.001$, Wilcoxon's test, Table 2).

During the first 5–6 minutes following SA and vasopressor administration until skin incision, mean SBP values were similar in Groups E and P. During the delivery, and at the fifth and 10th minute after delivery, and up to the end of the procedure, significantly higher mean SBP values were recorded in Group E compared to Group P (p < 0.001, Figure 1A).

Table 2. Hemodynamic changes between/within the two groups: ephedrine (E) and phenylephrine (P) vasopressors

Parameter	Baseline values		p^{EP}	During vasopressor infusion		p^{EP}	E	P
	Group E (n = 29)	Group P (n = 31)		Group E (n = 29)	Group P (n = 31)		p^{12}	p^{12}
SBP (mmHg)	122 (12)	121 (12)	0.828	122 (21)	114 (15)	< 0.001*	0.938	0.006*
DBP (mmHg)	74 (9)	73 (11)	0.685	66 (15)	61 (15)	< 0.001*	0.005*	< 0.001*
CO (L/min)	8 (2)	8 (2.2)	0.645	11 (3.7)	9 (3.5)	< 0.001*	< 0.001*	0.424
SV (mL)	91 (26)	88 (22)	0.668	111 (36)	110 (38)	< 0.001*	0.002*	0.001*
SVR (dyn s/cm^5)	878 (204)	852 (233)	0.643	671 (291)	777 (366)	< 0.001*	< 0.001*	0.253
HR (bpm)	93 (23)	97 (18)	0.444	97 (21)	83 (16)	< 0.001*	0.333	< 0.001*

SBP – systolic blood pressure; DBP – diastolic blood pressure; CO – cardiac output; SV – stroke volume; SVR – systemic vascular resistance; HR – heart rate; p^{12} – baseline values compared with values during vasopressor infusion in the respective group
*significant p < 0.05, mean (sd) Student's t test

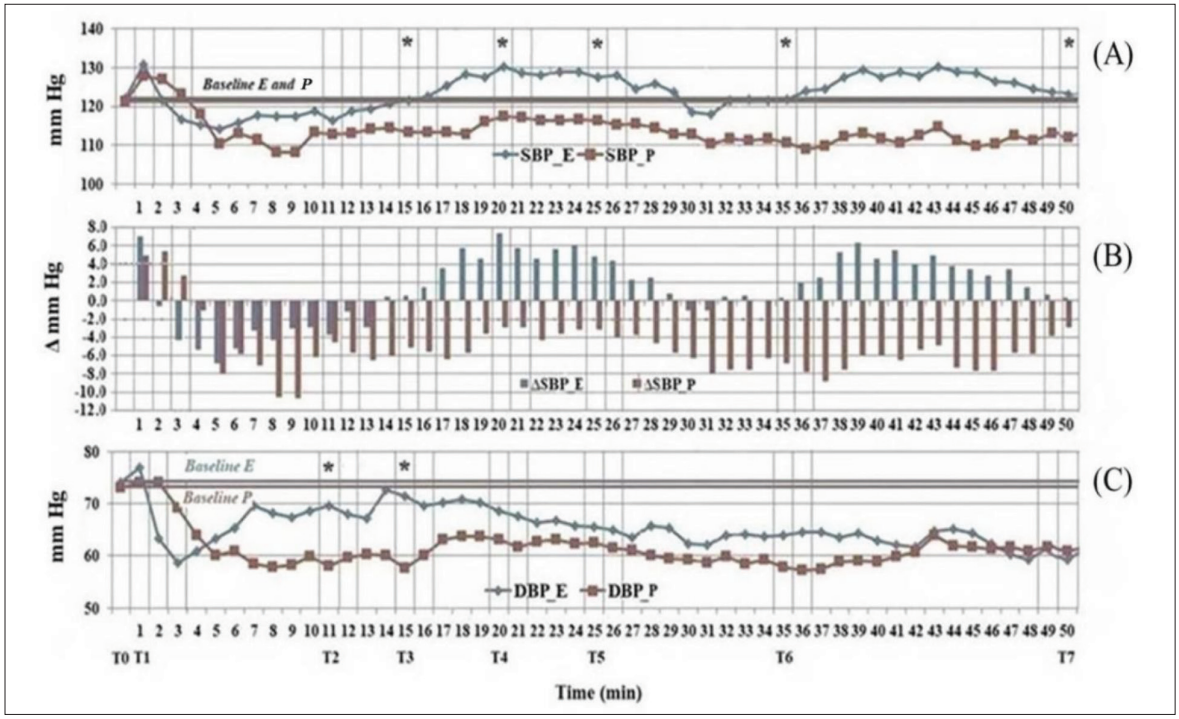

Figure 1. Changes in hemodynamic parameters; comparison to baseline values, and values after spinal anesthesia/after administration of vasopressors; SBP-1A – systolic blood pressure; ΔSBP-1B – average changes of systolic blood pressure; DBP-1C – diastolic blood pressure; T0 – start of infusion P; T1 – spinal anesthesia (both groups) and start of ephedrine infusion; T2 – skin incision (both groups); T3 – delivery (both groups); T4 – five minutes after delivery; T5 – 10 minutes after delivery; T6 – 20 minutes after delivery; T7 – end of surgery
*significant p-values

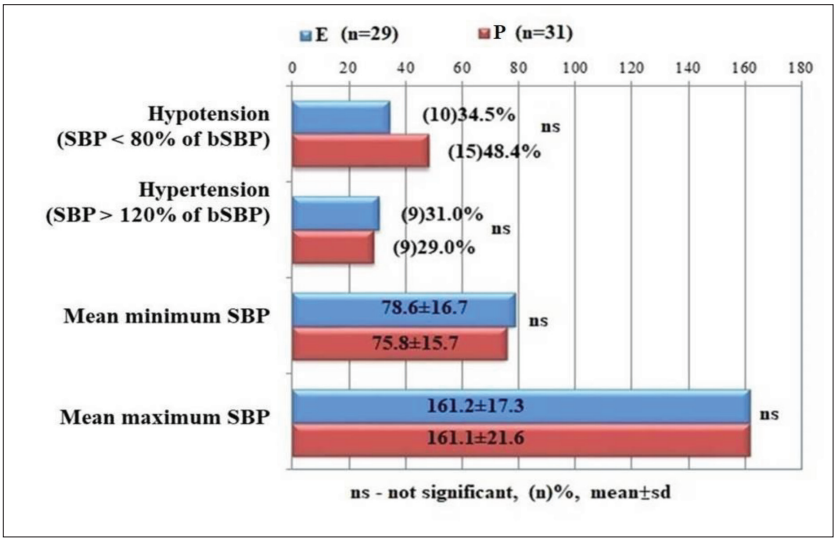

Figure 2. Incidence of hypotension/hypertension and mean minimum/maximum systolic arterial pressure; SBP – systolic blood pressure; bSBP – baseline systolic blood pressure

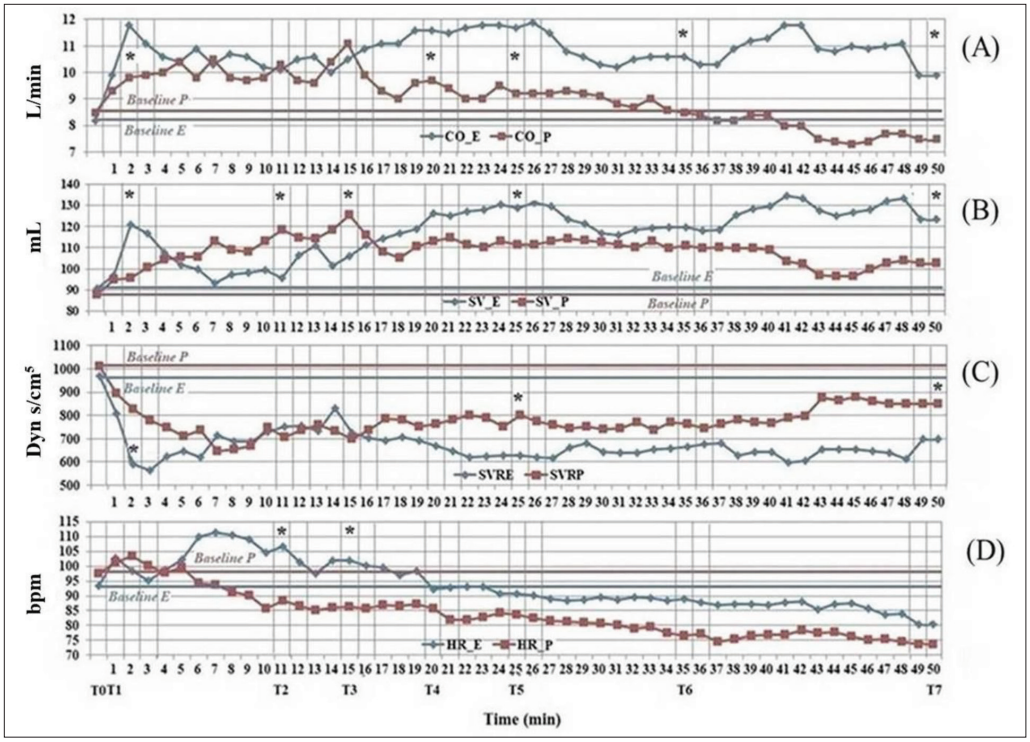

Figure 3. Changes in hemodynamic parameters, before (baseline) and after spinal anesthesia/after administration of vasopressors; CO-3A – cardiac output; SV-3B – stroke volume; SVR-3C – systemic vascular resistance; HR-3D – heart rate; T0 – start of phenylephrine infusion; T1 – spinal anesthesia (both groups) and start of ephedrine infusion; T2 – skin incision (both groups); T3 – delivery (both groups); T4 – five minutes after delivery; T5 – 10 minutes after delivery; T6 – 20 minutes after delivery; T7 – end of operation;

*significant p-values

In Group P, except in the first few minutes, SBP was lower than baseline. The largest decrease in SBP was seen after 8–9 minutes of phenylephrine infusion, but average values were only about 10 mmHg lower than baseline (Figure 1B). There was a decrease of SBP in Group E between 3–13 minute up to 6.5 mmHg (Figure 1B). Mean values of DBP in both groups were lower than basal levels (Figure 1C).

No significant differences in the incidence of hypotensive and hypertensive episodes were detected, and the average minimum and maximum SBP were similar between groups (Figure 2).

Mean CO values in Group E were consistently higher than baseline after SA and up to the end of the surgical procedure. In Group P, mean CO values were higher than baseline only up to the 36th minute (Figure 3A). After SA, during the second minute, mean values of CO in Group E increased significantly compared to the baseline, and compared to Group P ($p < 0.001$, Figure 3A).

After delivery and up to the end of the procedure, lower mean Group P CO values were recorded compared to those in Group E (Figure 3A). However, mean Group P CO values were similar to baseline values. After the 36th minute, (20 minutes away from delivery), and up to the end

Table 3. Intraoperative characteristics, umbilical vein gases and Apgar scores

Variables	Group E (n = 29)	Group P (n = 31)	p
Intraoperative characteristics			
Time from spinal anesthesia to the end (min)	49 (8)	51 (9)	0.291
Duration of I–D (min)	15 (3)	15 (3)	0.982
Vasopressor infusion duration (min)	23 (6)	50 (15)	< 0.001**
Sensor block level before skin incision	T5 (T4–T6)	T5 (T4–T6)	-
Modified Bromage score for motor block	3 (3–4)	3 (3–4)	-
Number of patients received rescue bolus doses (%)	7 (24%) dose 5–15 mg	7 (23%) dose 0.05–0.15 μg	0.887
Number of rescue bolus doses	13	11	-
Number of rescue bolus doses before delivery	10	7	-
Number of rescue bolus doses after delivery	3	4	-
Mean doses of vasopressors (mg)	49.3 (9.3)	1.3 (0.4)	-
Total fluid-crystalloid (ml)	1551 (244)	1419 (291)	0.061
Incidence of nausea			
Yes	7 (24%)	3 (10%)	0.133
No	22 (76%)	28 (90%)	
Incidence of vomiting			
Yes	1 (3%)	0 (0%)	0.297
No	28 (97%)	31 (100%)	
Medicaments			
Atropine			
Yes	1 (3%)	7 (23%)	0.029*
No	28 (97%)	24 (77%)	
Metoclopramide			
Yes	7 (24%)	3 (10%)	0.133
No	22 (76%)	28 (90%)	
Umbilical vein gases and Apgar scores			
pH	7.36 (7.14, 7.49)	7.36 (7.29, 7.45)	0.668
PO2 (mmHg)	27.3 (24.4, 30.5)	27.7 (26.1, 28.8)	0.657
PCO2 (mmHg)	37.3 (32.7, 41.8)	38.2 (32.6, 42.6)	0.706
BE (mEq/L)	-3.8 (-4.7, -1.6)	-2.6 (-4.0, -1.1)	0.122
Apgar first minute	8.97 (0.19)	8.90 (0.30)	0.342
Apgar fifth minute	9.93 (0.26)	9.87 (0.34)	0.447

I–D – time from the induction of spinal anesthesia to delivery of the baby; pH – acidity; PO_2 – partial oxygen pressure; PCO_2 – partial carbon dioxide pressure; BE – base excess
*significant $p < 0.05$, mean (sd), n (%), Students t-test, χ^2 test, pH, PO_2, PCO_2, BE median (min., max. range), Apgar mean (sd); Modified Bromage score: 1 – able to raise legs above the table; 2 – able to flex knees; 3 – able to move feet only; 4 – no movement in legs or feet

of the procedure, mean values of Group P CO decreased compared with baseline. In Group E, CO was significantly higher up to the end of the procedure compared with baseline and Group P, ($p < 0.001$, Figure3A).

Both vasopressors increased SV. In Group E, SV increased significantly after SA, with the addition of ephedrine infusion in the second minute ($p < 0.001$, Figure 3B). During skin incision and delivery, SV was significantly higher in Group P compared to Group E ($p < 0.001$, Figure 3B). From that point on, Group E had higher SV than Group P until the end of the procedure.

SVR values were lower than baseline in both groups (Figure 3C).

After five minutes of infusion, Group E's HR was increased above baseline up to 20th minute. After 24th min, mean HR of Group E was below baseline, but it was consistently higher than mean HR of Group P (Figure 3D). HR was higher at skin incision and delivery in Group E ($p < 0.001$, Figure 3D). Mean Group P HR was below baseline from the fifth minute up to the end of the procedure.

Mean values of vasopressors infusion duration were significantly longer ($p < 0.001$, Student's t-test, Table 3) in Group P compared with Group E.

Incidence of nausea and vomiting were similar in both groups. The administration of atropine was significantly higher in Group P ($p = 0.029$, χ^2 test, Table 3).

Umbilical venous pH was lower than 7.2 in one case in Group E. However, the mean pH values in both groups were identical (7.36). No newborn had Apgar score lower than 8 in the first minute, and mean values of Apgar score were similar between groups. Gas analysis of umbilical vein showed no significant differences between Groups E and P.

DISCUSSION

In our study, after SA, CO values increased along with concomitant increase of HR and SV. Liu et al. [17] detected a significant decrease in SVR and an increase in CO after SA both before administration of phenylephrine and before hypotension occurred.

In our study, phenylephrine infusion was introduced two minutes prior to administration of SA. This was followed by an increase in CO following SA, as noted above, but these changes were significantly lower than in Group E where ephedrine infusion was given immediately after SA. With both phenylephrine and ephedrine, the drop in SBP did not exceed 20% and the changes were relatively minor.

We have shown that patients from Group E had significantly higher SBP, DBP, CO, SV, and HR, but lower SVR than in Group P. Similarly, Gunda et al. [18] in their study showed that HR was also significantly higher using ephedrine *vs.* phenylephrine. However, they used a single bolus dose of 5 mg of ephedrine or 100 μg of phenylephrine, but both were administered only after the occurrence of hypotension. Furthermore, the same authors did not detect significant differences in SBP (although slightly higher in Group P than in Group E) [18].

Allen et al. [19] investigated four groups of patients who received different doses of prophylactic fixed-rate phenylephrine infusions. In the groups that received 25 μg/min. and 50 μg/min. P, SBP was higher than 80% of baseline and

in the groups that received 75 μg/min. and 100 μg/min. the incidence of hypertension was increased [19]. Also, our study showed that patients who received phenylephrine at a dose of 25 μg/min., SBP remained greater than 80% of baseline.

Langesæter et al. [20] examined the effects of two different intrathecal doses of bupivacaine, with or without iv phenylephrine infusion on hemodynamic parameters. This study showed that a low dose of prophylactic phenylephrine infusion (0.25 μg/kg per min.) provided the best hemodynamic stability [20]. In our study, patients in Group P received 10 mg spinal bupivacaine and prophylactic phenylephrine infusion (25 μg/min.) two minutes prior to SA and were also quite effective.

Mon et al. [21] in their study examined the effects of ephedrine and phenylephrine infusion on hemodynamics. In Group P, CO was significantly lower than the baseline in the 10th and 15th min. after application of SA, in contrast with Group E, in which CO values were not significantly changed [21]. Ephedrine administration was associated with significantly more cases of fetal acidosis despite good SBP control and increased CO [21]. Our study showed that after the initial increase in CO in both groups, there was a reduction in CO in the Group P, but values below the baseline were detected only from 36th minute up to the end of the surgery, which might be important for fetal outcome. It should be recalled that the dose of phenylephrine in our study was four times lower than in the previously described and continued for a longer time. Unlike in the previously mentioned study, where no significant changes in SV were detected, in our study SV was increased in both groups [21]. Numerous studies have shown associations between HR and CO, as was the case here [14].

The lowest average HR values in Group P were recorded in the 37th minute of phenylephrine infusion, which coincides with the time when CO in the same group drops below baseline values. A total of seven patients in Group P had HR < 60 and received atropine (five of them before delivery), which may be associated with the administration of seven phenylephrine rescue doses before the birth of a baby. Also, other authors have found higher incidence of bradycardia in patients receiving phenylephrine than those receiving ephedrine [22].

Ngan et al. [23] showed that prophylactic phenylephrine infusion of 100 μg/min. decreased the incidence of hypotension during SA for cesarean delivery compared with control group, who received bolus phenylephrine at 100 μg after each event of SBP < 80% of baseline. Results in our study, using four times smaller dose of phenylephrine infusion, show that reactive hypertension was recorded in 29% of the patients.

Although other studies reported higher incidences of nausea and vomiting in groups on ephedrine, we did not detect significant differences between Group E and Group P [10, 19]. We are of the opinion that not only type of vasopressor, but the protocol of administration and dosage significantly influences the incidence of side effects.

CONCLUSION

In this study, SBP remained in the normal range during infusion in both groups, which indicated that ephedrine and phenylephrine are both effective. Both vasopressors had similar effects on newborns. Continuous monitoring of hemodynamic parameters, with a well-defined administration protocol and dosing regimen are considered important for a favorable outcome, as shown in this study.

Conflict of interest: None declared.

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Поређење ефикасности и безбедности преемптивних протокола инфузије ефедрина и фенилефрина – превенција хипотензије и утицај на хемодинамске параметре током спиналне анестезије за царски рез

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САЖЕТАК

Увод/Циљ Током спиналне анестезије (СА) за царски рез долази до значајних хемодинамских промена, као и до хипотензије.

Циљ ове студије био је да се утврде и упореде ефикасност и безбедност преемптивних инфузионих протокола два најчешће коришћена вазопресора, ефедрина (група Е, $n = 29$) и фенилефрина (група П, $n = 31$), не само у циљу превенције хипотензије већ ради утврђивања њиховог утицаја на хемодинамске параметаре, као што су ударни волумен и минутни волумен, коришћењем континуираног неинвазивног хемодинамског монитора.

Методе Инфузија ефедрина је укључена у дози од 5 *mg/min.*, одмах после СА. Инфузија фенилефрина је укључена у дози од 25 *μg/min.*, на два минута пре СА.

Резултати У групи Е средње вредности систолног крвног притиска и срчана фреквенција нису се значајно промениле у односу на базалне вредности. Минутни волумен је био значајно виши ($p < 0,001$), док је системски васкуларни отпор био значајно нижи у односу на базалне вредности ($p < 0,001$). У групи П средње вредности систолног крвног притиска и дијастолног крвног притиска биле су значајно ниже у односу на базалне вредности ($p = 0,006$, односно $p < 0,001$). Средње вредности систолног крвног притиска, дијастолног крвног притиска, минутног волумена, ударног волумена, системског васкуларног отпора и срчане фреквенције су се статистички значајно разликовале између група Е и П ($p < 0,001$). Гасне анализе венске умбиликалне крви и оцена Апгар су биле сличне у обе групе.

Закључак Вазопресори ефедрин и фенилефрин су веома делотворни у превенцији хипотензије током СА.

Кључне речи: царски рез; спинална анестезија; ефедрин; фенилефрин; хипотензија; хемодинамски параметри