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Paper Accepted* **ISSN Online 2406-0895**

Original Article / Оригинални рад

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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

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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Received: June 7, 2019
Revised: January 24 2020
Accepted: January 27, 2020
Online First: February 12, 2020
DOI: https://doi.org/10.2298/SARH190607009V

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

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When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

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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

SUMMARY

Introduction/Objective Spinal anesthesia (SA) for cesarean section may lead to the 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 2 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, systemic vascular resistance (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

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 утврди и упореди ефикасност и безбедност преемптивних инфузионих протокола два најчешће коришћена вазопресора, ефедрина (Група Е, Н = 29) и фенилефрина (Група П, Н = 31), не само у циљу превенције хипотензије, већ ради утврђивања њиховог утицаја на хемодинамске параметаре, као што је ударни волумен (УВ) и минутни волумен (МВ) коришћењем континуираног неинвазивног хемодинамског монитора.

Методе Инфузија ефедрина је укључена у дози од 5 *mg*/*min* одмах након СА. Инфузија П је укључена у дози од 25 *μg*/*min*, на 2 *min* пре СА.

Резултати У групи Е, средње вредности систолног крвног притиска (СКП) и срчана фреквенција (СФ) се нису значајно променили у односу на базалне вредности. МВ је био значајно виши ($p < 0.001$), док је системски васкуларни отпор (СВО) био значајно нижи у односу на базалне вредности ($p < 0.001$). У П групи, средње вредности СКП и дијастолног крвног пристиска (ДКП) биле су значајно ниже у односу на базалне вредности ($p = 0.006$, односно $p < 0.001$). Средње вредности СКП, ДКП, МВ, УВ, СВО и СФ су се статистички значајно разликовале између Е и П групе ($p < 0.001$). Гасне анализе венске умбиликалне крви као и Апгар скор су били слични у обе групе.

Закључак Е и П вазопресори су веома ефективни у превенцији хипотензије током СА.

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

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 (DO_2) to organs and tissues, results in buildup of oxygen debt [7, 8, 9], causing complications after SA. 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 areephedrine 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 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 spinal anesthesia.

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 recruited 60 patients (from June 25, 2017 to April 25, 2018) divided randomly into Group P and Group E. Each patient 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 less than 50kg or greater than 100 kg, height less than 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 P 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 P iv. If bradycardia occurred together with SBP less than 20% below baseline, the infusion of P 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, P infusion was discontinued. If SBP exceeded 20% of baseline the infusion of P was discontinued.

Protocol E group

Group E patients received E 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 baseline. If SBP fell by greater than 20% of baseline, a rescue bolus dose of 5 mg E was given iv. Where SBP was greater than 20% of baseline, E infusion was discontinued. Both infusions were administered via infusion pump (Argus 600S Argus Medical AG, CH 3627 Heimberg).

Bradycardia was defined as a heart rate less than 60 per min while hypotension was defined as a reduction in SBP greater than 20% of baseline. Hypertension represents increase of SBP greater than 20% above baseline.

All patientsreceived50 mg of ranitidine iv and were pre-loaded with 500 ml of Hartmann's solution. During the cesarean section the infusion of Hartmann's solution was resumed. BP, HR, electrocardiogram (ECG), and oxygen saturation (SpO_2) were recorded using the DASH® 4000 monitor (GE Medical Systems Information Technologies,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). The Pulse CO^{R} algorithm is used for calculating SV from the BP waveform using pulse power analysis, and the parameters were measured continuously up to the end of the surgical procedure. It provides a nominal value for SV, CO and SVR using patient demographic data of height, weight and age. Spinal anesthesia was

given in the sitting position using a" pencil point" spinal needle of 25G (Pencan® B.Braun, Melsungen AG, Germany). The patients received bupivacaine-spinal 0.5%2.0-2.2ml in theL3/4 intervertebral space. The patients were then returned to the previous supine position with the operating table tilted to the left side 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 1 and 5 minutes was recorded for each newborn. The time from spinal injection to baby delivery and the time from SA to 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 19.0 IBM Corporation. Before the beginning of the study, we performed 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. Body weight and height which 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 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 two groups (baseline values[1], 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 with Group P, while mean SVR was significantly lower in the Group E compared with the Group P (Table 2).

During E infusion the mean DBP was significantly lower compared with baseline values ($p^{12} = 0.005$, Wilcoxon's test, Table 2). Mean values of CO and SV were significantly

higher during E infusion compared with 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 the mean values of CO and SVR were not significantly changed during the infusion compared with the baseline values. During P 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 with 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 min. following SA and vasopressor administration until skin incision, mean SBP values were similar in Groups E and P. During delivery and at the 5th and 10th min. after delivery and up to the end of the procedure, significantly higher mean SBP values were recorded in Group E compared with Group P ($p < 0.001$, Figure 1A).

In Group P, except in the first few minutes, SBP was lower than baseline. The largest decrease in SBP was seen after8-9 min of P infusion but average values were only about 10 mmHg lower than baseline (Figure 1B). In Group E there was a decrease of SBP between 3–13 min. 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). During the 2nd min, after SA mean values of CO in Group E increased significantly compared with baseline, and compared with 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 with Group E (Figure 3A). However, mean Group PCO values were similar to baseline values. After the 36th minute, (20 min from the delivery), and up to the end 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 ESV increased significantly after SA and E in fusion in the 2nd minute ($p < 0.001$, Figure 3B).During skin incision and delivery SV was significantly higher in Group P compared with Group E ($p < 0.001$,Figure 3B).From that point 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 5 minutes of infusion, Group E HR was increased above baseline up to 20th minute. After 24th min, mean Group E HR were below baseline, but mean Group E HR was consistently higher than mean Group PHR (Figure 3D). HR was higher in Group Eat skin incision and delivery ($p < 0.001$, Figure 3D). Mean Group P HR was below baseline from the 5th min. 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 the Group E. However, the mean pH values in both groups were identical (7.36). No newborn had Apgar score lower than 8 in the 1st minute and mean values of Apgar score were similar between groups. Gas analysis of umbilical vein showed no significant differences between the 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(P) and before hypotension occurred.

In our study, P infusion was commenced 2 min 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 the Group E where ephedrine (E) infusion was given immediately

after SA. With both P and E 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 E versus P. However, they used a single bolus dose of 5 mg E or 100 μg of P, 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 P than in E group) [18].

Allen et al. [19] investigated four groups of patients who received different doses of prophylactic fixed-rate P infusions. In the groups that received 25μg/min and 50μg/min P, SBP was higher than 80% of baseline and in the groups that received 75μg/min and 100μg/min the incidence of hypertension was increased [19]. Also, our study showed that patients who received P at a dose of 25μg/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 intravenous P infusion on hemodynamic parameters. This study showed that low dose of prophylactic P infusion (0.25μg/kg per min) provided the best hemodynamic stability [20]. In our study, patients in Group P received 10 mg spinal bupivacaine and prophylactic P infusion (25 μg/min) 2 minutes prior to SA and were also quite effective.

Mon et al. [21] in their study examined the effects of E and P infusion on hemodynamics. In Group P CO was significantly lower than baseline in the 10^{th} and15^{th} min after application of SA, in the contrast to E group in which CO values were not significantly changed [21]. Despite good SBP control and increased CO with E, its administration was associated with significantly more cases of fetal acidosis [21].Our study showed that after the initial increase in CO in both groups, there was a reduction in CO in the P group, but values below the baseline were detected only from 36^{th}min up to the end of the surgery, which might be important for fetal outcome. It should be recalled that the dose of P in our study was 4 times lower than in the previously described and continued for a longer duration. Unlike in the previously mentioned study [21], where no significant changes in SV were detected, here SV was increased in both groups. Numerous studies have shown associations between HR and CO [14], as was the case here.

The lowest average HR values in the P group were recorded in the 37th minute of P infusion, which coincides with the time when CO in the same group drops below baseline values. A total of 7 patients in P group had HR < 60 and received atropine (five of them in the period prior to the birth of the baby), which may be associated with the administration of 7 P rescue doses in the period prior to the birth of a baby. Also, other authors have found higher incidence of bradycardia in patients receiving P than those receiving E [22].

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

We did not detect significant differences between E and P groups in nausea and vomiting, although other studies reported higher incidences in E groups [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 E and P 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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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;

*significant $p < 0.05$, mean (sd), median (min–max. range), n (%), Student's t-test, χ^2test

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 (2.0)	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*

p^{12} – baseline values compared with values during vasopressor infusion in the respective group
*significant $p < 0.05$, mean (sd) Student's t test;

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

Variables	Group E (n = 29)	Group P (n = 31)	p
Intraoperative characteristics			
Time from SA 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 recieved rescue boluse 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
PO_2 (mmHg)	27.3 (24.4, 30.5)	27.7 (26.1, 28.8)	0.657
PCO_2 (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 1st min.	8.97 (0.19)	8.90 (0.30)	0.342
Apgar 5th min.	9.93 (0.26)	9.87 (0.34)	0.447

*significant $p < 0.05$, mean (sd), n (%), Students t-test, χ^2 test, I-D-time from the induction of spinal anesthesia to delivery of the baby, pH, PO_2, PCO_2, BE median (min., max. range), Apgar mean (sd)

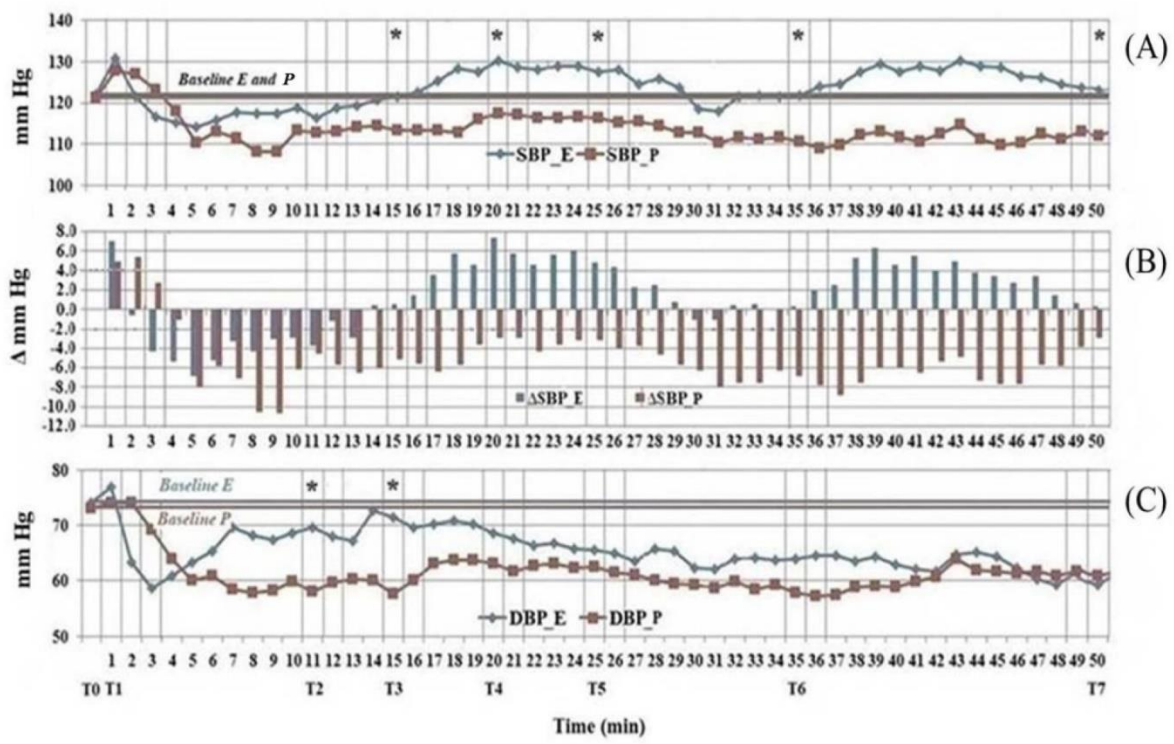

Figure 1. Changes in hemodynamic parameters; systolic blood pressure (SBP-1A), average changes of SBP (ΔSBP-1B), diastolic blood pressure (DBP-1C), comparing to baseline, and after spinal anesthesia/after administration of vasopressors (E and P); T0 – start of infusion P; T1 – spinal anesthesia (Groups E and P) and start of infusion E; T2 – skin incision (Groups E and P); T3 – delivery (Groups E and P); T4 – 5 min. after delivery; T5 – 10 min. after delivery, T6 – 20 min. after delivery;T7 – end of surgery;
*significant p-values

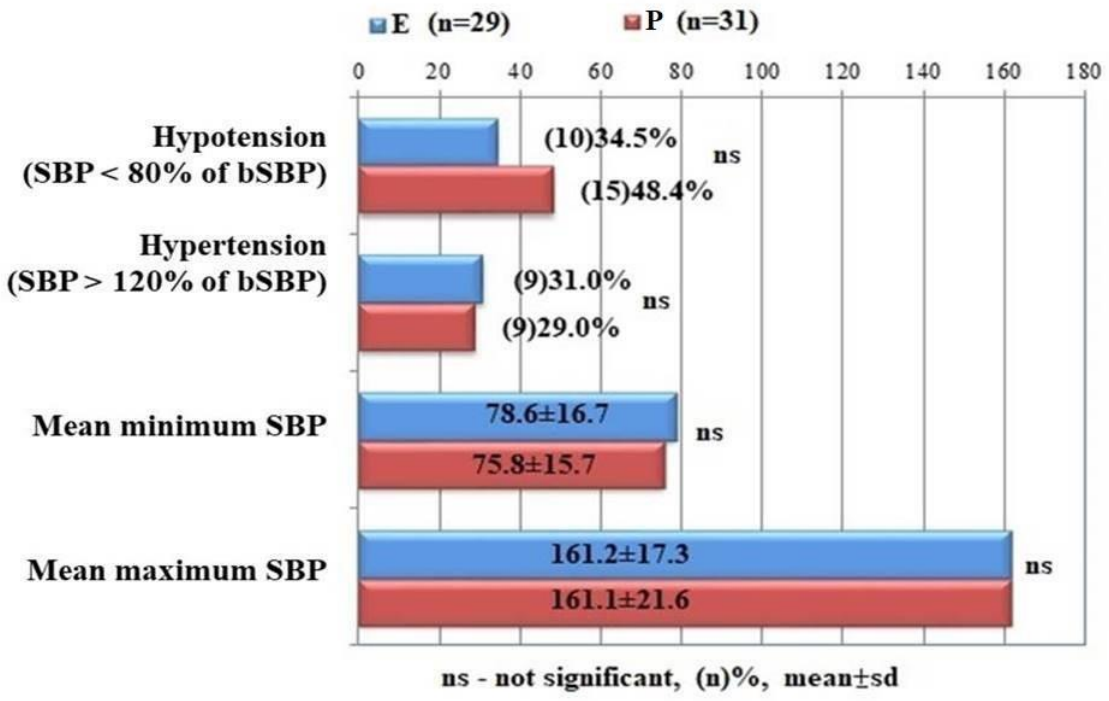

Figure 2. Incidence of hypotension/hypertension and mean minimum/maximum systolic arterial pressure; SBP – systolic blood pressure; bSBP – baseline systolic blood pressure

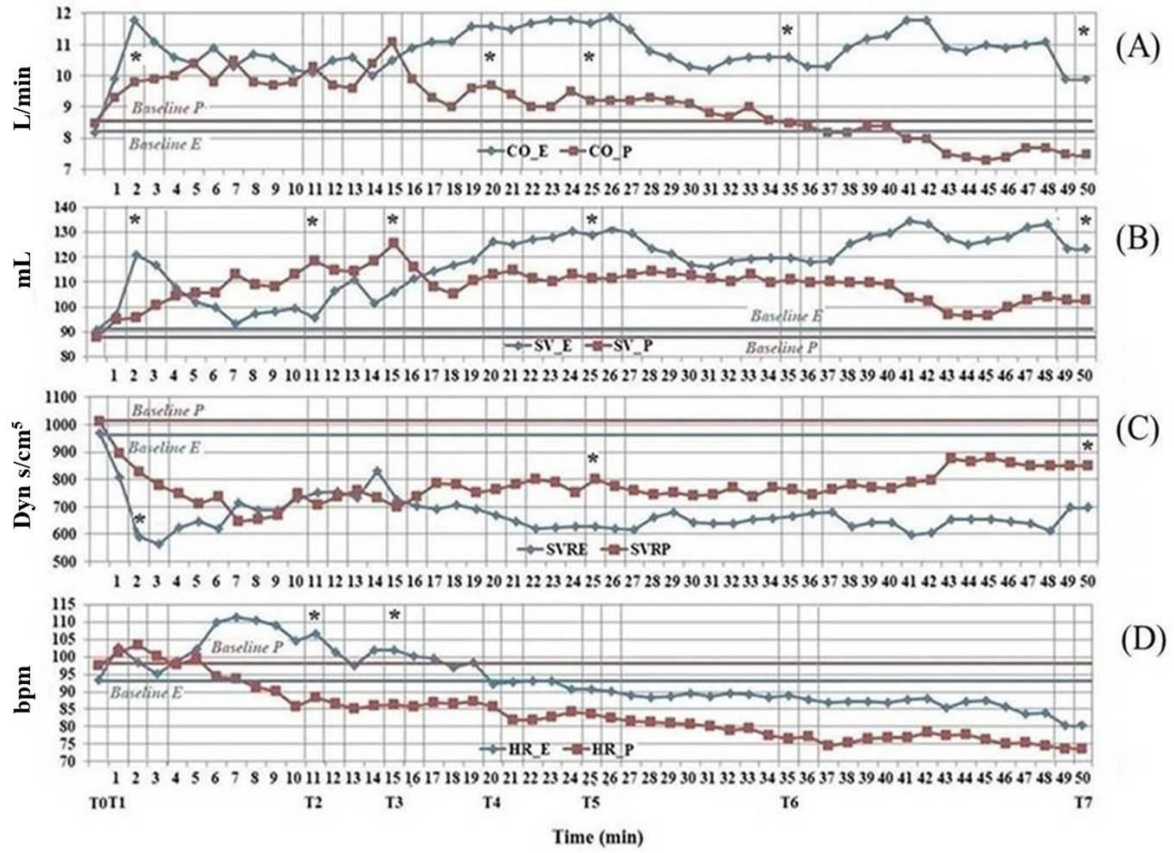

Figure 3. Changes in hemodynamic parameters; cardiac output (CO-3A), stroke volume (SV-3B), systemic vascular resistance (SVR-3C), heart rate (HR-3D), before (baseline) and after spinal anesthesia/after administration of vasopressors (E and P); T0 – start of infusion P; T1 – spinal anesthesia (Groups E and P) and start of infusion E; T2 – skin incision (Groups E and P); T3 – delivery (Groups E and P); T4 – 5 min. after delivery; T5 – 10 min. after delivery; T6 – 20 min. after delivery; T7 – end of operation;

*significant p-values

