ATATÜRK ÜNİVERSİTESİ YAYINLARI
ATATURK UNIVERSITY PUBLICATIONS

Research Article *Araştırma Makalesi* DOI: 10.61745/tss.1671431

Effects of Norepinephrine-Ephedrine Combination on Maternal Hemodynamics in Cesarean Sections Performed Under Spinal Anesthesia

Spinal Anestezi ile Yapılan Sezaryenlerde Norepinefrinin-Efedrin Kombinasyonunun Maternal Hemodinami Üzerine Etkileri

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ABSTRACT

Objective: The frequency of maternal hypotension after spinal anesthesia in Caesarean section (CS) may be as high as 90%. The aim of this study was to investigate the effect of the use of the combination of ephedrine and norepinephrine on maternal hemodynamics, neonatal APGAR and acidosis in CS delivery under spinal anesthesia.

Methods: This prospective, randomized, double-blind study included pregnant patients aged 18 - 45 years, evaluated as ASA class I-II for surgery, who underwent elective CS under spinal anesthesia. The clinical and laboratory findings, umbilical blood gases, maternal blood pressure and heart rate were also analyzed. The patients were randomly separated into 3 groups: Ephedrine (E), Ephedrine+Norepinephrine (EN), and Norepinephrine (N).

Results: Umbilical cord venous blood pH and HCO_3 was lower in Group EN than the other groups. APGAR score was lower in Group E. Heart rate in Groups EN and N decreased up to the middle of surgery, then was slightly elevated until the end of surgery. Heart rate persistently decreased in Group E from the beginning to the end of the surgery. SBP decreased significantly at the end of the surgery compared to basal levels in Group EN and N, and did not decrease significantly in Group E.

Conclusion: These findings suggest that the addition of norepinephrine to ephedrine might increase the risk of fetal acidosis and affect the APGAR score. The longer duration of action and the higher number of bolus of ephedrine might be associated with a lesser decrease in maternal blood pressure after the middle of the surgery.

Keywords: Post-spinal hypotension, vasopressor, norepinephrine, ephedrine, caesarean section

ÖZ

Amaç: Spinal anestezi sonrası sezaryen doğumlarda (CS) maternal hipotansiyon sıklığı %90'a kadar çıkabilmektedir. Bu çalışmanın amacı, spinal anestezi altında gerçekleştirilen sezaryen doğumlarda epinefrin ve norepinefrin kombinasyonunun maternal hemodinami, yenidoğan APGAR skorları ve asidoz üzerindeki etkilerini araştırmaktır.

Yöntem: Bu prospektif, randomize, çift kör çalışma; spinal anestezi altında elektif sezaryen geçiren, cerrahi için ASA sınıf I-II olarak değerlendirilen 18-45 yaş arasındaki gebeleri içermektedir. Klinik ve laboratuvar bulguları, umbilikal kan gazları, maternal kan basıncı ve kalp atış hızı analiz edilmiştir. Hastalar rastgele üç gruba ayrılmıştır: Epinefrin (E), Epinefrin+Norepinefrin (EN) ve Norepinefrin (N) grupları.

Bulgular: Umbilikal kord venöz kan pH ve HCO_3 seviyeleri EN grubunda diğer gruplara göre daha düşük bulunmuştur. APGAR skoru, E grubunda daha düşük saptanmıştır. EN ve N gruplarında kalp hızı ameliyatın ortasına kadar azalmış, ardından ameliyat sonuna

Received/ Geliş Tarihi	08.01.2025
Revision request/Revizyon Talebi	03.02.2025
Son Revizyon/Last Revision	04.02.2025
Accepted/Kabul Tarihi	17.02.2025
Publication Date/Yayın Tarihi	08.04.2025

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Cite this article: Soyalp C, Yüzkat N, Kurt N, Gülhaş N. Effects of Norepinephrine-Ephedrine Combination on Maternal Hemodynamics in Cesarean Sections Performed Under Spinal Anesthesia. *Trends Surg Sci*. 2025;4(1):1-10.

kadar hafif bir artış göstermiştir. E grubunda kalp hızı ameliyatın başından sonuna kadar sürekli azalma göstermiştir. EN ve N gruplarında sistolik kan basıncı (SKB), ameliyat sonunda başlangıç seviyelerine kıyasla anlamlı olarak azalmış, E grubunda ise anlamlı bir azalma gözlenmemiştir.

Sonuç: Bu bulgular, epinefrine norepinefrin eklenmesinin fetal asidoz riskini artırabileceğini ve APGAR skorunu etkileyebileceğini göstermektedir. Epinefrinin daha uzun etkili olması ve daha fazla bolus uygulanması, ameliyatın ortasından itibaren maternal kan basıncındaki azalmanın daha az olmasına katkıda bulunabilir.

Anahtar Kelimeler: Post-spinal hipotansiyon, vazopressör, norepinefrin, efedrin, sezaryen

INTRODUCTION

Caesarean section (CS) is a commonly used route of delivery for pregnant patients with some compelling indications and the rates of CS are increasing in patients with these indications. Anesthesiologists have a responsibility to take immediate care of the patient's safety and ensure optimal conditions during surgery. However, in CS procedures, the anesthetic given to the mother also affects the fetus. Hence, the safety and stability of the fetus becomes important in addition to that of the mother. The choice of the anesthesia method and anesthetic agent to be used is of great importance during CS.[1]

Anesthesia-related complications are the leading cause of maternal morbidity and mortality in CS with the most common reason in those applied with general anesthesia being failure of intubation and pulmonary aspiration of gastric content.[2] As a result of maternal mortality during general anesthesia, regional anesthesia has been increasingly used during CS.[3] The leading cause of mortality in regional anesthesia is due to the higher level of neural block and local anesthetic toxicity.[4] Following the introduction of regional anesthesia, the rates of anesthesia-related maternal mortality in CS procedures have decreased.[5]

There are several advantages of regional anesthesia such as a lower risk of aspiration with protection of airway reflexes and spontaneous respiration, lower risk of neonatal resuscitation, earlier initiation of breast-feeding, better postoperative analgesia, *less* postoperative vomiting, and early recovery of gastrointestinal motility.[6]

However, there are also some risks of this procedures. Bradycardia due to a higher level of block, decreased venous return and systemic vascular resistance due to medical sympathectomy may cause the development of maternal hypotension during surgery.[7] The frequency of maternal hypotension after spinal anesthesia may be as high as 90%. Nausea, vomiting, spinal cord ischemia, fetal acidosis and a lower APGAR score may also be observed after spinal anesthesia. Fetal acidosis and a lower APGAR score may result from compromised uteroplacental blood flow.

Therefore, it is important that maternal hypotension isavoided and the maternal hemodynamic status should be stabilized in pregnant patients during spinal anesthesia.[8] To prevent maternal hypotension as much as possible, preoperative and intraoperative intravenous crystalloid infusion, and vasoactive substances have been used. Several vasoactive medications such as norepinephrine, ephedrine, or phenylephrine have been examined in previous studies. However, there are few studies regarding the use of norepinephrine in obstetric patients. To the best of our knowledge, the effect of the combination of ephedrine and norepinephrine on maternal and fetal hemodynamics during Cesarean delivery under spinal anesthesia is not known and has not been studied to date. The aim of this study was to investigate the effect of the use of ephedrine and norepinephrine combined and alone on maternal hemodynamic parameters, neonatal APGAR and blood gas parameters in CS delivery under spinal anesthesia.

METHODS

The study was approved by the Van Yüzüncü Yıl University Local Institutional Ethics Committee with an approval number of June 6, 2018 decision no: 08, and was initiated after it was recorded with the clinical trial number of NTC03672071. Written informed consent was obtained from all subjects. The study included pregnant patients aged between 18 and 45 years, evaluated as ASA class II for surgery, who underwent elective CS under spinal anesthesia. The study was designed as a prospective, randomized, double-blinded study. Patients for whom elective CS was initiated under spinal anesthesia and was then changed to general anesthesia were excluded. Patients were also excluded if they were ASA class III or IV, had a twin or multiple pregnancy, if emergency CS was performed, and those who were hemodynamically unstable, had cardiac or pulmonary disorders, placenta previa, placental detachment, intrauterine fetal death, syndromic fetus, intrauterine growth retardation, preeclampsia, or a known history of allergy to ephedrine and/or norepinephrine. The newborn infants who were intubated in the postpartum period for any reason were also excluded. The physical

Table 1. Demographic data,nause-vomiting,irrability and headache

	E	EN	N	*P*
	(n=33)	(n=29)	(n=28)	
Age (years)	30.48±6.09	29.21±5.29	30.18±6.28	,681
Height (cm)	160 (150 / 176)	162 (151 / 180)	160 (155 / 170)	,602
Weight (kg)	80 (60 / 120)	80 (60 / 100)	71 (55 / 90)	.066
BMI	30.07 (23.44 / 44.08)	29.38 (20.76 / 35.16)	27.34 (19.84 / 35.16)	.111
Gravida	2 (1 / 8)	4 (1 / 8)	3 (1 / 6)	.245
Duration of surgery (mins)	38 (22 / 68)	36 (28 / 60)	34 (20 / 56) [AB]	**.047**
Number of drug boluses given n (%)				
I	12 (36.4)	14 (48.3)	14 (50.0)	.170
II	7 (21.2)	6 (20.7)	10 (35.7)	
III	14 (42.4)	9 (31.0)	4 (14.3)	
ASA score				
I	14 (42.4)	11 (37.9)	24 (85.7) [AB]	**<.001**
II	19 (57.6) [C]	18 (62.1) [C]	4 (14.3)	
Nausea-vomiting				
Absent	25 (75.8)	23 (79.3)	22 (78.6)	.949
Present	8 (24.2)	6 (20.7)	6 (21.4)	
Irritability				
Absent	32 (97.0)	28 (96.6)	24 (85.7)	.238
Present	1 (3.0)	1 (3.4)	4 (14.3)	
Headache				
Absent	26 (78.8)	25 (86.2)	27 (96.4)	.138
Present	7 (21.2)	4 (13.8)	1 (3.6)	

Datas were expressed as a mean±SD, number and percentage. OneWay ANOVA (RobustStatistic:Brown-Forsythe), Kruskal Wallis Test(Monte Carlo), Post Hoc Test : Dunn's Test, Fisher Freeman Halton (Monte Carlo), Pearson Chi Square Test(Monte Carlo); Post Hoc Test: Benjamini-Hochberg correction, [A] Significant for ephedrine group, [B] Significant for norepinephrine + ephedrine group, [C] Significant for norepinephrine group

examination and clinical findings, and laboratory parameters of the patients were evaluated, recorded and analyzed. Fetal blood gas analyses were recorded. Blood pressure and heart rate parameters of the patients were analyzed and compared. All patients were evaluated 30 minutes preoperatively. A large venous line was opened and 10 mL/kg crystalloid fluid was given to all patients intravenously in the preoperative evaluation room. The patients were monitored, and the hemodynamic parameters of heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and oxygen saturation (SpO_2) were recorded preoperatively.

A total of 97 patients were initially evaluated and 7 were excluded from the study as they did not meet the criteria. Thus 90 patients were included and analyzed in the study. The patients were randomly separated into 3 groups according to the vasoactive agents applied during surgery, as the Ephedrine (E) group, theEphedrine+Norepinephrine (EN) group, and the Norepinephrine (N) group.

Spinal Anesthesia: Asepsis and antisepsis were first provided, then by palpating the L3-L4 spinal space, a Quincke injector was inserted into this space. A fixed dose of 12.5 mg 0.5% isobaric bupivacaine was injected into the subarachnoid space via the injector guide after cerebrospinal fluid drainage was seen. The spinal injector was withdrawn, and a pressured medical dressing was applied. The patient was positionedon the surgical table which was tilted 15˚ to the left. Continuous nasal oxygen of 2L/min was given to the patient via a nasal cannula. The level of dermatome was checked by hot-coldtest then when the block level arrive T4 surgery was initiated. All surgigal procedures were performed by same surgen.

Table 2. Blood gas values and APGAR score

	E (n=33)	EN (n=29)	N (n=28)	*P*
Venous				
pH	7.38 (6.96 / 7.49)	7.32 (6.9 / 7.44) [AC]	7.41 (6.51 / 7.54)	**.002**
PCO2	37.1 (9.3 / 70)	34.7 (7.1 / 49)	35.3 (21.6 / 92.7)	.528
PO2	15.4 (3.4 / 97.8)	16.25 (3.6 / 102.3)	17.85 (9 / 99.1)	.325
HCO3	20.8 (-4.1 / 27.1)	15.8 (1.9 / 23.1) [AC]	21.9 (1.8 / 36.4)	**.001**
BE	-1.7 (-27.9 / 23.8)	-11.6 (-29.9 / 2.5) [AC]	-1.95 (-23.6 / 9.5)	**.002**
Arterial				
Ph	7.4 (6.97 / 7.49)	7.32 (6.98 / 7.58)	7.42 (6.96 / 7.61) [B]	**.037**
PCO2	32.9 (7 / 51)	32.4 (6 / 52.5)	31.75 (9.3 / 48.2)	.707
PO2	21.8 (5.9 / 101)	18 (10.4 / 108.3)	26.75 (12.2 / 108.5)	.258
HCO3	20.8 (6.1 / 29.4)	16.5 (5.4 / 27.5)	21.75 (5 / 29.3)	.052
BE	-2.9 (-28.2 / 7.6)	-10.2 (-29.5 / 4.5)	-2.2 (-29.4 / 8.1)	.056
APGAR score				
1 min	7 (5 / 8) [BC]	8 (7 / 8)	8 (5 / 8)	**<.001**
5 mins	8 (6 / 9) [BC]	9 (8 / 9)	9 (7 / 9)	**.001**
(5-1) mins	1 (1 / 3)	1 (1 / 1)	1 (1 / 2)	.173
P (intragroups)	**<.001**	**<.001**	**<.001**	

Datas were expressed as a mean±SD, number and percentage. Kruskal Wallis Test(Monte Carlo), Post Hoc Test: Dunn's Test, Wilcoxon Signed Ranks Test(Monte Carlo),

[A] Significant for ephedrine group, [B] Significant for norephedrine + ephedrine group, [C] Significant for norephedrine group

Hemodynamic parameters were recorded every 2 minutes during surgery using non-invasive methods. To maintain cerebral perfusion pressure when MBP began to decline by > 20% compared to the baseline level, an intravenous bolus of 5 mg ephedrine was given to the E group, 5 mcg norepinephrine to the N group, and 5 mg ephedrine + 2.5 mcg norepinephrine to the EN group. The number of bolus ofvasoactive agents used in all groups, side effects such as nausea, vomiting, irritability and headache, APGAR at 1st and 5th minutes, blood gas parameters in cord blood, and duration of surgery were recorded and analyzed. The drugs used in the study were obtained as norepinephrine bitartrate, 1 mg/ml (Levophed®, Hospira, Inc., Lake Forest, IL, USA), and ephedrine sulfate, 50 mg/ml (Ephedrine Sulfate®, Akorn, Inc., India).

The patients were randomly separated into the 3 groups using the closed envelope method, and the study was designed as a double-blinded,randomize dstudy. The drugs used in the study were prepared by a physician not involved in any other part of the study. This physician held the code for randomization and group allocation.

Statistical Analysis

Data obtained in the study were analysed statistically using SPSS 25.0(IBM Corporation, Armonk, NY, USA) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001. Paleontological statistics) software. The conformity of the univariate data to normal distribution was evaluated using the Shapiro-Wilk test, and homogeneity of variance was evaluated with theLevene test. The conformity of the multivariate data to normal distribution was evaluated using the Mardia; (Dornik and Hansenomnibus) test, and homogeneity of variance was evaluated with theBox'm test. When comparing multiple independent groups according to quantitative variables as parametric tests, One-Way Anova was used, and Fisher's Least Significant Difference (LSD) test was used for Post Hoc analysis. As non-parametric tests, the Kruskal-Wallis H test was used with the Monte Carlo Simulation technique, and Dunn's Test was used for Post Hoc analysis. When comparing repeated measurements of dependent quantitative variables, the Wilcoxon Signed Ranks test was used. When examining the interaction of repeated measurements of these variables according to the groups, the General Linear Model-Repeated Anova test and Friedman's Two-Way test were used, with Dunn's Test and the Bonferroni test applied for Post Hoc analysis. When comparing groups according to categorical variables, the Pearson Chi Square and Fisher-Freeman-Holton tests were applied with the Monte Carlo Simulation technique, the

Table 3. Hemodynamic paramaters

	E (n=33)	EN (n=29)	N (n=28)	*P*
Heart Rate				
Basal	93.48±15.96	96.93±18.80	92.61±18.81	.627
Mid-surgery	90.12±14.57	87.83±15.88	88.61±15.74	.837
End of surgery	87.55±14.14	91.66±16.32	90.71±14.33	.526
P (intragroups)	**,131**	**.063**	**.176**	
Mid-basal	-3.36±18.00	-9.10±19.51	-4.00±12.06	.356
End -basal	-5.94±17.81	-5.28±17.20	-1.89±17.03	.633
End-mid	-2.58±10.55	3.83±13.72	2.11±12.21	.108
SAP				
Basal	117.18±18.55	123.48±21.75 [3]	125.11±20.65 [2 3]	.275
Mid-surgery	112.62±13.39	112.91±15.38	109.66±15.64	.658
End of surgery	113.18±13.26	111.62±17.96	104.07±15.32	.065
P (intragroups)	,383	**.025**	**<.001**	
Mid-basal	-4.56±18.35	-10.57±23.23	-15.45±19.92	.125
End -basal	-4.00±18.12[C]	-11.86±21.50	-21.04±18.63	**.004**
End-mid	0.56±9.80	-1.29±13.87	-5.59±14.20	.174
DAP				
Basal	64.85±12.99 [2 3]	72.24±15.18 [2 3]	68.07±12.27 [2 3]	.106
mid	56.41±8.35	59.34±9.82	57.21±10.59 [3]	.478
End	57.09±11.38	56.76±12.49	51.04±10.08	.079
P (intragroups)	**.004**	**<.001**	**<.001**	
Mid-basal	-8.44±13.39	-12.90±17.99	-10.86±14.67	.529
End -basal	-7.76±14.66 [C]	-15.48±16.28	-17.04±15.62	**.046**
End-mid	0.68±11.04	-2.59±12.63	-6.18±12.40	.092
Mean				
Basal	84.85±14.87 [2]	92.69±20.45 [3]	88.93±15.41 [2 3]	.204
Mid	76.67±9.10	82.19±10.51	78.73±10.46 [3]	.102
End	78.64±11.53	78.97±13.85	71.93±11.06	.053
P (intragroups)	**,017**	**.006**	**<.001**	
Mid-basal	-8.18±15.17	-10.50±22.62	-10.20±16.51	.864
End -basal	-6.21±16.16	-13.72±21.06	-17.00±16.75	.063
End-mid	1.97±11.16 [C]	-3.22±12.07	-6.80±11.27	**.014**
SPO_2				
Basal	98 (96 / 99) [3]	98 (94 / 100) [3]	98 (92 / 100) [2 3]	.462
Mid	98.5 (96 / 100)	98.5 (96 / 100)	99 (96 / 100)	.417
End	99 (96 / 100)	99 (97 / 100)	99 (97 / 100)	.779
P (intragroups)	**,011**	**.014**	**.001**	

Mid-basal	0.5 (-2 / 4)	1 (-4 / 4)	1 (-3 / 7)	0.369
End -basal	1 (-3 / 4)	1 (-1 / 4)	1 (-1 / 7)	0.787
End-mid	0 (-2 / 2)	0 (-1 / 3)	0 (-2 / 2)	0.597

General Linear Model Two-Way ANOVA(Univariate) (Method:Bootstrap); Post Hoc Test: Bonferroni, Friedman Test(Monte Carlo), Kruskal Wallis Test(Monte Carlo), Post Hoc Test : Dunn's Test,

[A]Significant for ephedrine group, [B]Significant for norephedrine + ephedrine group, [C]Significant for norephedrine group, [1] Significant for Basal, [2] Significant for mid-surgery, [3] Significant for end of surgery

column rates were compared with each other and were expressed according to Benjamini-Hochberg corrected p value results. Quantitative variables were stated asmean±standard deviation (SD) and median (minimum/maximum) values, and categorical variables were stated as number(n) and percentage (%) in the tables. Variables were evaluated with a 95% confidence level, and a value of $P < .05$ was accepted as statistically significant.

RESULTS

Mean age was similar in all the groups. There was no difference between the groups in respect of height, weight, BMI and gravida. The duration of surgery was the shortest in Group N ($P = .047$), and was longer in Group EN than in Group N ($P = .044$), and longer in Group E than in Group N ($P = .024$) (Table 1). The number of boluses of vasoactive drug was similar in all the groups. The rate of patients with ASA I score was higher in Group N than in Group E and EN ($P < .001$). The frequency of nausea-vomiting, irritability and headache was similar in all the groups.

Umblical cord venous blood pH was lower in Group EN than in Group E ($P = .047$), and Group N ($P < .001$). Venous blood HCO_3 was lower in Group EN than in Group E ($P = .011$), and Group N ($P < .001$). Umblical cord arterial blood pH was lower in Group EN than in Group N ($P = .013$) (Table 2). The 1-min APGAR score was lower in Group E than in Group NE ($P = .002$), and Group N ($P < .001$). The 5-min APGAR score was lower in Group E than in Group NE ($P = .012$), and Group N ($P < .001$). The difference between the APGAR scores at the 1st and 5th minutes was significant in each group.

The basal heart rate, heart rate in the middle and at the end of the surgery, and the change in heart rate were similar in all the groups, with no significant change determined in any group. In Groups EN and N, the heart rate decreased until the middle of surgery, then increased slightly until the end of surgery. A persistent decrease in heart rate from the beginning to the end of the surgery was determined in Group E. SBP decreased significantly at the end of the surgery compared to basal levels in Groups EN ($P = .025$) and N ($P < .001$), and did not decrease significantly in Group E. The decrease in SBP at the end of the surgery compared to the basal level was significantly higher in Group N than in Group E ($P = .001$). DBP was similar in all groups at baseline, in the middle and at the end of the surgery. DBP decreased significantly during surgery in all groups. The decrease in DBP at the end of the surgery compared to the basal level was significantly higher in Group N than in Group E ($P = .022$). MBP was similar in all groups at baseline, in the middle and at the end of the surgery. MBP decreased significantly during surgery in Groups EN and N. In Group E, mean MBP decreased in the middle of the surgery compared to the basal level, then increased slightly to wards the end of the surgery. The change in MBP at the end of the surgery compared to the middle of the surgery in Group E was significantly different from that of Group N ($P = .004$) (Table 3). There was no difference between the groups in respect of any of the measured SpO_2 levels.

DISCUSSION

As a summary of the findings of this study, umbilical cord venous blood pH and HCO3, and arterial pH were lower in Group EN than in Groups E and N. The APGAR score at the 1st and 5th minutes was lower in Group E than Groups EN and N. The APGAR score increased at the 5th minute compared to the 1st minute in all groups. Heart rate at baseline, in the middle and at the end of the surgery was similar in all groups and did not change during the surgery in any group. Maternal SBP decreased at the end of the surgery compared to baseline in Groups EN and N. Maternal DBP decreased significantly during the surgery in all groups, and to a greater extent in Group N than in Group E. Maternal MBP was similar in all groups at baseline, in the middle and at the end of the surgery. Maternal MBP decreased significantly during the surgery in Groups EN and E. However, in Group E, maternal MBP decreased in the middle of the surgery compared to baseline, then increased slightly towards the end of the surgery.

Elnabtity et al. investigated 122 patients undergoing elective CS under spinal anesthesia, and randomized them into ephedrine and norepinephrine groups according to vasoactive agent used during surgery.[9] The number of hypotensive episodes were observed to be higher in the

ephedrine group (n=61) than in the norepinephrine group (n=61) (P = .02). In that study, only systolic blood pressure was analyzed, and no study group was formed using a combination of ephedrine and norepinephrine to treat hypotension during CS. In the current study, maternal SBP did not decrease in Group E, whereas it decreased in Group EN and more so in Group N at the end of the surgery, but the difference was not statistically significant. Ephedrine is known to be the first-choice drug to prevent maternal hypotension.[10] It has a stimulant effect on both α and β adrenoceptors and therefore positive inotropic and chronotropic effects.[11] Repeated application of ephedrine may cause a decrease in the vasoconstrictive effect.[12] Norepinephrine causes α1 and β1 stimulation and maintains maternal blood pressure with a less negative effect on heart rate.[11,13] However, to the best of our knowledge, the combined effect of ephedrine and norepinephrine on maternal hemodynamics has not yet been studied in the literature. It was expected that the decrease in SBP could be less in Group EN than E. In contrast to this expectation, SBP was maintained only in the ephedrine (E) group. Ephedrine is known to have an effect of releasing endogenous norepinephrine. As the dosage of norepinephrine was lower in Group EN than in Group N, it can be assumed that this finding resulted from the emergence of physiological antagonism of ephedrine and norepinephrine on adrenoceptors. Maternal DBP and MBP were also evaluated and analyzed in addition to SBP. Maternal MBP in Group E first decreased during the surgery, then increased towards the end of surgery. This may be explained by the fact that ephedrine has a slower onset and longer duration of action than norepinephrine, and that the duration of the surgery was longest in Group E.[12,14] However, the patients could not be separated into different groups according to the duration of surgery. It might be postulated that the longer duration of surgery was associated with the higher mean blood pressure in Group E.

Elnabtity also showed that the number of boluses of vasoactive agents were higher in ephedrine group (P = .005).[9] Similarly in the current study, the percentage of higher number of boluses of vasopressor was the highest in Group E, albeit statistically non-significant. The number of boluses of vasopressor was associated with the number of hypotensive episodes. At the beginning of the surgery, the slower onset of action of ephedrine might have caused repeated hypotensive episodes and a need for additional vasopressor in Group E. The greater number of bolus in Group E might have led to a cumulative effect of ephedrine and the subsequent release of endogenous norepinephrine, and hence the smaller decrease in MBP at the end of surgery. Consequently, longer duration of surgery and a higher number of bolus of ephedrine might be associated with a lesser decrease in maternal SBP, DBP and MBP after the middle of the surgery.

In the last decade, phenlyephrine was the first choice to treat hypotension that developed during spinal anesthesia.[15] However, baroreceptor-mediated bradycardia caused by phenlyephrine might decrease cardiac output.[16] This is an especially important concern in obstetrics medicine, because of the risk of compromised uteroplacental blood flow. Kee et al. Showed that the normalized cardiac output value was greater in a norepinephrine group than in those given phenlyephrine, in a series of 104 pregnant patients applied with CS under spinal anesthesia and computer-controlled infusion of vasopressor.[11] In another study, the estimated dose equivalent to phenlyephrine 100 microgram was found to be norepinephrine 8 microgram to maintain blood pressure during CS under spinal anesthesia.[17] Sharkey et al. showed that the number of bradycardia episodes was lower in a norepinephrine group compared to a phenlyephrine group, when equipotent doses of drugs were used in CS under spinal anesthesia.[18] Elnabtity et al. showed that the frequency of bradycardia and tachycardia was less in a norepinephrine group than in an ephedrine group (P = .0002 and P = .008, respectively).[9] In the current study, the heart rate in Groups EN and N decreased until the middle of surgery, then elevated slightly until the end of surgery, whereas in Group E, there was a persistent decrease from the beginning to the end of the surgery. These findings may be explained by the beta 1 and weak beta 2 stimulatory effect of norepinephrine.[19] The activation of these receptors results in norepinephrine having a lesser negative effect on heart rate.

Uteroplacental blood flow is directly associated with maternal blood pressure, so maternal hypotension should be avoided and treated promptly to prevent fetal acidosis.[13,20] In the current study, umbilical cord venous blood pH and HCO_3, and arterial blood pH were significantly lower in Group EN. However, APGAR scores were the lowest in Group E. The use of ephedrine is known to maintain uterine blood flow[11], although the use of norepinephrine, as an alpha agonist, might compromise uteroplacental blood flow. However, Minzter et al. demonstrated that uteroplacental blood flow was not compromised after norepinephrine and it had no significant effect on fetal perfusion.[21] In the current study, the uterine artery pulsatility index was not evaluated. A previous study, has shown it to be lower in a norepinephrine group compared to an ephedrine group.[9] In the same study, APGAR scores at the 1st and 5th minutes were similar in both the ephedrine

and norepinephrine groups. The APGAR score is a subjective scoring system applied by the caregiver in the 1st and 5th minutes after delivery. Umbilical cord blood gas analysis may provide more objective knowledge about the neonatal health than the APGAR score. Therefore, based on the knowledge that norepinephrine might compromise the uteroplacental blood flow by alpha agonistic activity, it can be expected that Group N would have the lowest umbilical blood pH. Although the dosage of norepinephrine was lower in Group EN than Group N, the highest ratio of acidosis was observed in Group EN. There are multiple possible factors affecting the parameters of umbilical cord blood gas. Fetal blood gas also provides earlier information than the 1 and 5-min APGAR scores. In addition, the APGAR score may also be affected by interventions performed in the delivery room. Phenlyephrine may cause bradycardia associated with baroreceptor activation in addition to strong vasopressor activity. Norepinephrine has been known to cause fewer episodes of bradycardia.[11] Kee et al. showed that the incidence of bradycardia episodes was higher in a phenylephrine group than in a norepinephrine group in CS under spinal anesthesia.[22] If a patient group administered with phenylephrine had been included in the current study, there could have been a comparison of umbilical cord blood gas analyses of that group with Group EN. One study investigated and compared the effects of ephedrine and phenylephrine to treat post-spinal hypotension in 104 pregnant patients undergoing elective CS.[23] Umbilical arterial and venous pH and base excess were lower, and lactate concentration was higher in the ephedrine group than in the phenlyephrine group in that study. Moreover, maternal arterial pH levels were similar in both groups. The authors concluded that there was a clinical association between the effect of ephedrine causing more fetal acidosis and the higher placental transfer of ephedrine compared to phenlyephrine. Ephedrine may cause fetal stimulation of beta adrenoceptors and metabolism, and thus acidosis may ensue in fetal tissues.[15,24] Therefore, although ephedrine is known to protect uterine blood flow, by stimulating fetal beta adrenoceptors it may cause a higher frequency of fetal acidosis.[11,23] These findings are compatible with the current study results as the highest ratio of fetal acidosis was observed in Group EN. When ephedrine, which causes fetal acidosis was combined with norepinephrine, which compromises uteroplacental blood flow, the maximum effect of fetal acidosis occurred in Group EN. Maternal blood pH was not correlated with fetal blood pH in that study.[23] There are many factors regulating maternal blood pH, and the same dosage of vasopressor is expected to cause a lesser degree of acidosis in the mother than in the fetus. Maternal blood gas analysis was not included in the current study.

Strength and Limitations

To the best of our knowledge, this is the first study in literature to have investigated the combined effect of ephedrine and norepinephrine on maternal hemodynamics in CS delivery under spinal anesthesia. Several studies have investigated the effect of spinal anesthesia on SBP in CS delivery. In the current study, DBO and MBP were evaluated and analyzed in addition to SBP. No analysis of the patients could be made according to the duration of surgery, and there was no evaluation of the uterine artery pulsatility index. If a patient group administered with phenylephrine had been included, it might have been possible to demonstrate a significant difference between the groups in respect of umbilical cord blood gas analyses. Maternal blood gas analysis was not included in the study.

CONCLUSION

The findings of this study suggest that the addition of norepinephrine to ephedrine might increase the risk of fetal acidosis and the APGAR score. The longer duration of action and the higher number of ephedrine boluses might be associated with a lesser decrease in maternal SBP, DBP and MBP after the middle of the surgery. However, heart rate consistently decreased from the beginning to the end of the surgery in the ephedrine group. In conclusion, there are several advantages and disadvantages of ephedrine and norepinephrine. The selection of vasopressor to prevent and treat post-spinal hypotension should be based on the cardiac and hemodynamic characteristics of each patient. There is a need for further studies to clarify the effect of the combination of ephedrine and norepinephrine on maternal hemodynamics and fetal health.

Etik Komite Onayı: Çalışmanın etik onayı 6 Haziran 2018 tarihinde Van Yüzüncü Yıl Üniversitesi Etik Kurulu'ndan alındı (Karar No. 08).
Hasta Onamı: Çalışma hakkında bilgi verildikten sonra tüm katılımcılardan yazılı bilgilendirilmiş onam alındı.
Hakem Değerlendirmesi: Dış bağımsız.
Yazar Katkıları: Fikir- CS; Tasarım-NG; Denetleme-NK; Kaynaklar-NY; Veri Toplanması ve/veya İşlemesi-NY; Analiz ve/ veya Yorum- NG; Literatür- NY; Yazıyı Yazan- CS: Eleştirel İnceleme- NK.
Çıkar Çatışması: Yazarlar, çıkar çatışması olmadığını beyan etmiştir.
Finansal Destek: Yazarlar, bu çalışma için finansal destek almadığını beyan etmiştir.

Ethics Committee Approval: Ethical approval for the study was obtained from the Van Yüzüncü Yıl University Ethics Committee on June 6, 2018 (Decision No. 08).
Informed Consent: Written informed consent was obtained from all participants after providing information about the study.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept – CS; Design – NG; Supervision – NK; Resources – NY; Data Collection and/or Processing – CS; Analysis and/or Interpretation – NG; Literature Search – NY; Writing

Manuscript – CS; Critical Review – NK

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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