Original Article/*Özgün Araştırma*

doi: 10.54875/jarss.2022.63497

Retrospective Evaluation of the Effect of Prophylactic Norepinephrine Infusion on Preventing Spinal Anesthesia Induced Hypotension During Cesarean Section

Profilaktik Norepinefrin İnfüzyonunun Sezaryenlerde Spinal Anesteziye Bağlı Hipotansiyonu Önlemedeki Etkisinin Retrospektif Değerlendirilmesi

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ABSTRACT

Objective: Maternal hypotension after spinal anesthesia is a frequent and important deleterious complication that requires treatment. Current study aims to evaluate the effectiveness of prophylactically administered norepinephrine infusion protocol in preventing spinal anesthesia induced hypotension in elective cesarean deliveries performed in our institue between November 2017 and April 2018.

Methods: Patients underwent cesarean section were evaluated retrospectively. They were divided into two groups as the norepinephrine group (n=32) and the control group (n=79), according to the treatment methods applied prophylactically to prevent spinal-induced hypotension. Patient demographics, 1st and 5th minutes APGAR scores, umbilical cord blood gas pH, newborn weight, overall amount of ephedrine used, adverse conditions such as maternal nausea and vomiting, systolic blood pressure, and heart rate were collected from the anesthesia records and medical electronic systems.

Results: Total of 111 patients were included in the analysis. There was no significant difference between umbilical artery pH values. The first (7.01 vs 7.34) minute mean APGAR scores in control group were significantly lower (p=0.008). The incidence of hypotension before delivery was lower in the norepinephrine group (40.6%) compared to the control group (74.7%) (p<0.05). The mean total dose of ephedrine was greater in the control group (13.67 vs 6.09 mg, p<0.01).

Conclusion: We believe that prophylactic norepinephrine infusion is effective in preventing spinal-induced hypotension for cesarean deliveries.

Keywords: Caesarean section, norepinephrine, obstetrical anesthesia, spinal anesthesia

ÖZ

Amaç: Sezaryenlerde spinal anesteziye bağlı hipotansiyon sık görülen ve tedavi gerektiren önemli bir komplikasyondur. Bu çalışmanın amacı, hastanemizde Kasım 2017-Nisan 2018 tarihleri arasında uygulanan elektif sezaryenlerde, profilaktik olarak uygulanmış olan norepinefrin infüzyonunun spinal anesteziye bağlı hipotansiyonu önlemedeki etkinliğini değerlendirmektir.

Yöntem: Sezaryen ameliyatı olan hastalar retrospektif olarak tarandı. Spinal anesteziye bağlı hipotansiyonu önlemek amacıyla profilaktik olarak uygulanmış tedavi yöntemlerine göre; norepinefrin grubu (n=32) ve kontrol grubu (n=79) olarak iki gruba ayrıldı. Hastaların demografik bilgileri, 1. ve 5. dakika APGAR skorları, kordon kan gazı pH değerleri, yenidoğan ağırlıkları, kullanılan toplam efedrin miktarı, annede bulantı kusma gibi yan etkiler, sistolik kan basıncı ve kalp atım hızı bilgileri anestezi kayıtlarından ve tıbbi elektronik sistemlerden alındı.

Bulgular: Toplam 111 hasta analiz edildi. Umbilikal arter pH değerleri arasında anlamlı bir fark yoktu. Birinci dakika ortalama APGAR skorları kontrol grubunda anlamlı derecede daha düşüktü (7,01'e karşı 7,34, p=0,008). Doğum öncesi hipotansiyon insidansı; norepinefrin grubunda (%40,6) kontrol grubuna (%74,7) kıyasla daha düşük bulundu (p<0,05). Ortalama toplam efedrin dozu kontrol grubunda daha yüksekti (13,67'ye karşı 6,09 mg, p<0,01).

Sonuç: Sezaryen doğumlarda spinal anesteziye bağlı hipotansiyonu önlemede profilaktik olarak norepinefrin infüzyonunun etkili olduğu kanaatindeyiz.

Anahtar sözcükler: Sezaryen, norepinefrin, obstetrik anestezi, spinal anestezi

Received/Geliş tarihi : 18.11.2021
Accepted/Kabul tarihi : 27.01.2022
Publication date : 28.04.2022

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Cite as: Ataibis S, Ozkan G, Senkal S, Kara U, Ince ME, Cosar A. Retrospective evaluation of the effect of prophylactic norepinephrine infusion on preventing spinal anesthesia induced hypotension during cesarean section. JARSS 2022;30(2):89-96.

INTRODUCTION

Maternal hypotension is the most common complication after spinal anesthesia for cesarean section (1). The incidence of postspinal hypotension in caesarean sections has been reported to be approximately 60% when no measures are taken (2,3). Therefore, the use of prophylactic vasopressors to prevent postspinal hypotension is popular in obstetric anesthesia (2). For a long time, maternal hypotension after spinal anesthesia has been treated with ephedrine as a first-choice drug. However, its side effects such as tachyphylaxis, tachycardia, and fetal acidemia limited its use. Since phenylephrine crosses placenta less than ephedrine, so it causes less fetal acidosis, which is one of the main reason for recommending the use of phenylephrine (4). However, phenylephrine is known as a potent alpha agonist; hence, it causes bradycardia, which limits its use especially in patients with a low baseline heart rate.

Recently, norepinephrine has just begun to be used in this field. Besides its alpha agonist activity similar to phenylephrine, it has weak beta agonist activity, prevents reflex bradycardia, and reduces cardiac output. The role of norepinephrine in the management of maternal hypotension has been demonstrated in several studies (5,6).

In the present study, we hypothesized that continuous prophylactic norepinephrine infusion protocol that was used for the last six months could have reduced the incidence of maternal hypotension in parturient underwent cesarean section with spinal anesthesia. We also investigated maternal side effects and neonatal outcomes as well as their effects on maternal hemodynamic parameters.

MATERIAL and METHODS

This single-center, retrospective cohort study was conducted in a tertiary hospital. It was approved by the Ethics Committee of Gulhane Training and Research Hospital (Date: 05.04.2018, No: 18/98). The current study included 235 women who underwent cesarean delivery with spinal anesthesia between November 2017–April 2018. Patients with respiratory disease, cardiovascular disease, pregnancy-induced hypertension, fetal anomalies, multiple pregnancy, and missing follow-up data were excluded. Obtaining informed consent from the patients was waived due to the retrospective nature of the study. The study was carried out in accordance with the Declaration of Helsinki.

Our institution's routine spinal anesthesia protocol for cesarean section includes standard monitorization and recording of the parameters (Electrocardiogram, heart rate, pulse oximetry, and noninvasive blood pressure), 500 mL 0.9% NaCl infusion for pre-loading, performing spinal block at midline approach between L3-L4 intervertebral space with a 25 G pencil-point needle using intrathecal 12.5 mg of hyperbaric bupivacaine and 25 µg of fentanyl.

In the control group (Group C) that did not receive prophylactic norephinephrine infusion, ephedrine (5 mg IV bolus) and atropine (0.5 mg IV) were planned to treat hypotension (if systolic blood pressure decreases ≥20% of the baseline value) and bradycardia (if heart rate< 50 bpm).

Norepinephrine diluted with 0.9% NaCl to reach a final concentration of 4 µg mL^{-1} was used in this study depending on the choice of the anesthesioloigst. All patients' data were obtained from the patient files and anesthesia records. According to these records norepinephrine infusion started at a rate of 30 mL h^{-1} just after intrathecal injection was adjusted with respect to the change in baseline systolic blood pressure (SBP) and ephedrine (5 mg IV bolus) was administered in patients with SBP below 80% of the baseline despite maximum rate of norepinephrine infusion (80 mL h^{-1}).

Seventy nine of 111 patients, 79 who did not receive norepinephrine infusion considered to be Group C, whereas 32 patients received norepinephrine infusion constituted the study group (Group N).

A decrease in SBP below 80% of the baseline value after spinal anesthesia until delivery was accepted as "*hypotension before delivery*". A decrease in SBP below 80% of the basal value after delivery was accepted as "*hypotension after delivery*". A decrease in heart rate below 50 bpm after spinal anesthesia was accepted as "*bradycardia"*. The number of patients with nausea/vomiting and the total amount of ephedrine used were also documented from anesthesia records.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS for MAC version 25.0 software. Mean±standard deviation, median, minimum and maximum, frequency and percentage values are used in descriptive statistics. The Kolmogorov-Smirnov test was used to consider the normal distribution of continuous variables. The Mann-Whitney U test was used for the comparison of continuous variables. The distribution of the categorical variables in the groups was compared using the Chi-Square test. Values of $p<0.05$ were considered statistically significant.

RESULTS

During the study period, 235 patients were evaluated for eligibility. In total, 111 patients were included in the analysis (Figure 1). When the groups were compared in terms of demographic features, there was a statistically significant difference only in terms of age (Table I) ($p<0.05$).

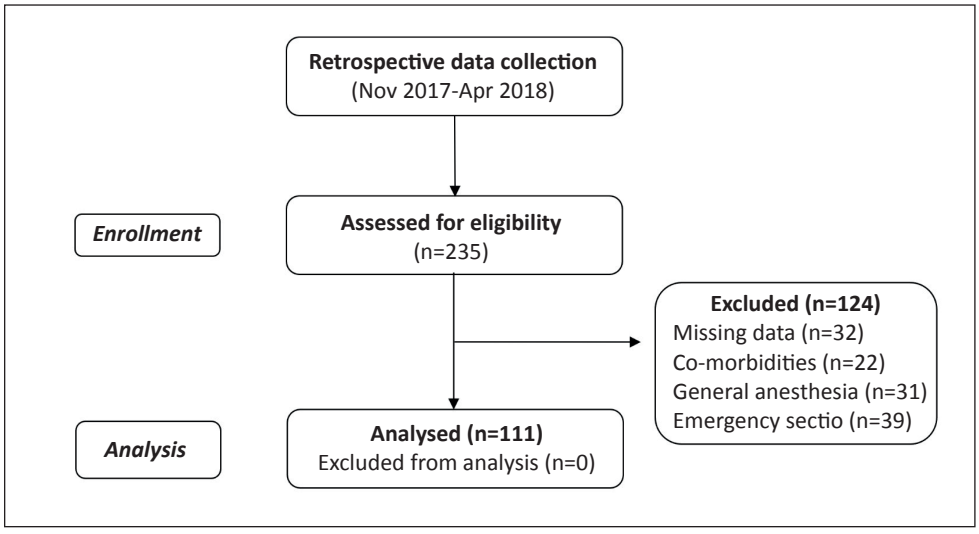

Figure 1. Study flow chart.

Table I. Patient Demographics

	Control group n=79	Norephinephrine group n=32	p
Age (years)	29.3±5.52	31.7±5.6	**0.02**
Height (cm)	162±5.7	161±5.9	0.4
Weight (kg)	78.2±10.4	78.4±12.6	0.9
BMI (kg m^{-2})	29.6±3.8	30.2±5.05	0.5
Gravida	2.15±0.89	2.4±1.1	0.2
Parity	1.8±0.76	2.09±0.8	0.2
Gestasyonel age (weeks)	38.6±0.94	38.5±0.9	0.5

Data are presented mean ± SD.

Neonatal outcomes are shown in Table II. While there was no significant difference in umbilical artery pH values between the groups, but birthweight was significantly lower in the control group than that of the study group (3227±400 vs 3388±426) ($p<0.05$). Newborns' APGAR scores were measured as a continuous variable and a categorical variable respectively. As a continuous variable, the 1st and 5th minute mean APGAR scores in the control group were significantly lower than the study group. There was a statistically significant difference in 1st minute APGAR scores as a categorical variable, but no difference in 5th minute APGAR scores. The SBP values measured at the 5th, 6th, 7th, and 10th minutes before delivery and 1st and 2nd minutes after delivery were significantly lower in the control group ($p<0.05$) (Figure 2, 3). Hearth rate (HR) values measured at the 3rd, 4th, 6th, 7th, 8th, 10th, and 11th minutes before delivery and 1st and 2nd minutes after delivery were significantly lower in the norepinephrine group ($p<0.05$) (Figure 4, 5). Furthermore, the HR in the norepinephrine group was markedly lower over time compared to the control group.

The perioperative characteristics of the groups are shown in Table III. The incidence of hypotension before delivery was significantly lower in the norepinephrine group ($p<0.05$). No difference was observed in the incidence of hypotension after delivery and bradycardia between groups. There was no difference between the groups in terms of the incidence of peroperative nausea and vomiting. The mean total dose of ephedrine was greater in the control group than in the study group (13.67 vs 6.09 mg) ($p<0.01$).

DISCUSSION

Our retrospective study demonstrated that prophylactically administered norepinephrine infusion was associated with fewer cases of hypotension and was beneficial for neonatal outcomes compared to the control group. It was also indicated that the total amount of therapeutic vasopressor that was used was lower in the norepinephrine group.

Lower APGAR scores are associated with impaired uteroplacental perfusion caused by postspinal hypotension (7). Therefore, the 1st and 5th minute APGAR scores in this

Table II. Neonatal Outcomes

	Control group n=79	Norephinephrine group n=32	p
Umblical arterial pH	7.35±0.03	7.36±0.03	0.6
Birth weight (gr)	3227±400	3388±426	**0.04**
APGAR score (1st min), (mean ± SD)	7.01±0.4	7.34±0.7	**0.008**
APGAR score (1st min), n (%)			
6	6 (7.6%)	1 (3.1%)	**0.014**
7	66 (83.5%)	22 (68.8%)	
8	7 (8.9%)	6 (18.8%)	
9	0 (0%)	3 (9.4%)	
APGAR score (5th min), (mean ± SD)	9.07±0.2	9.2±0.42	**0.035**
APGAR score (5th min), n (%)			
9	70 (88.6%)	28 (87.5%)	1.000
10	9 (11.4%)	4 (12.5%)	

Data are presented mean ± SD and n (%).

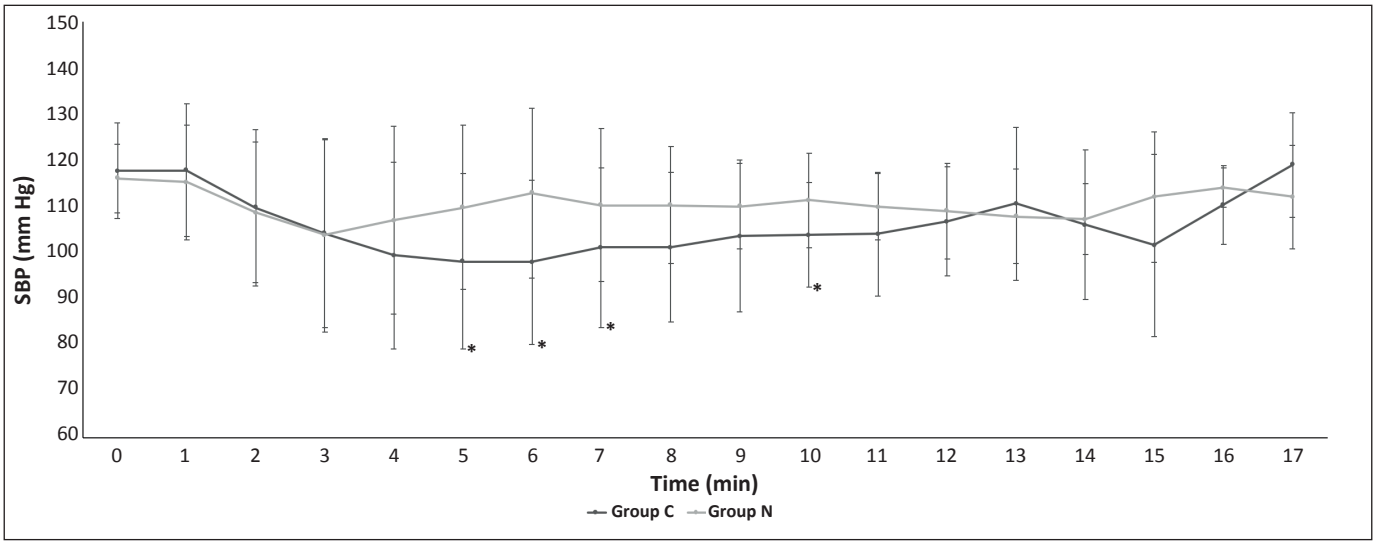

Figure 2. Changes in systolic blood pressure (SBP) before delivery. Markers are means and error bars are standard deviations. **Group C:** Control group; **Group N:** Norephinephrine group; ***:** p<0.05 compared to Group C.

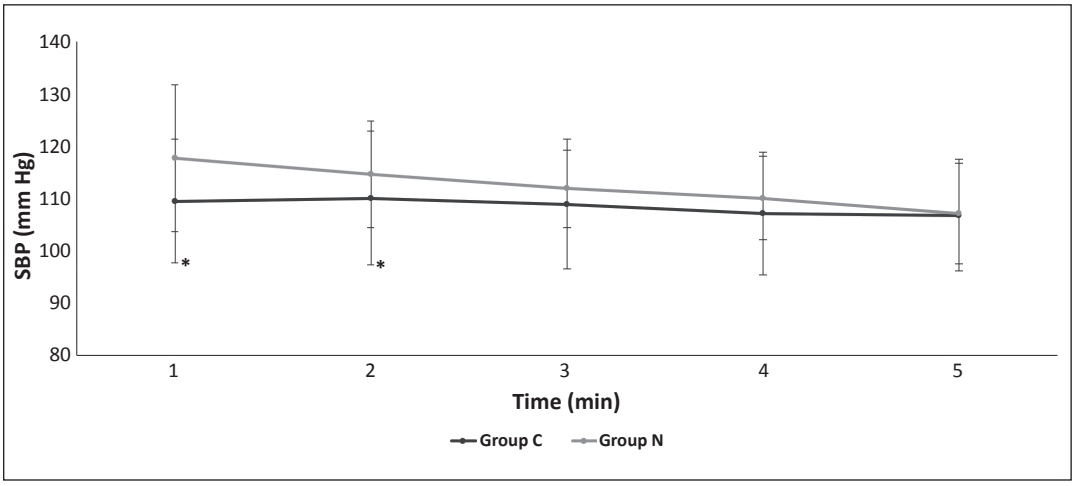

Figure 3. Changes in systolic blood pressure (SBP) after delivery. Markers are means and error bars are standard deviations. **Group C:** Control group; **Group N:** Norephinephrine group; ***:** p<0.05 compared to Group C.

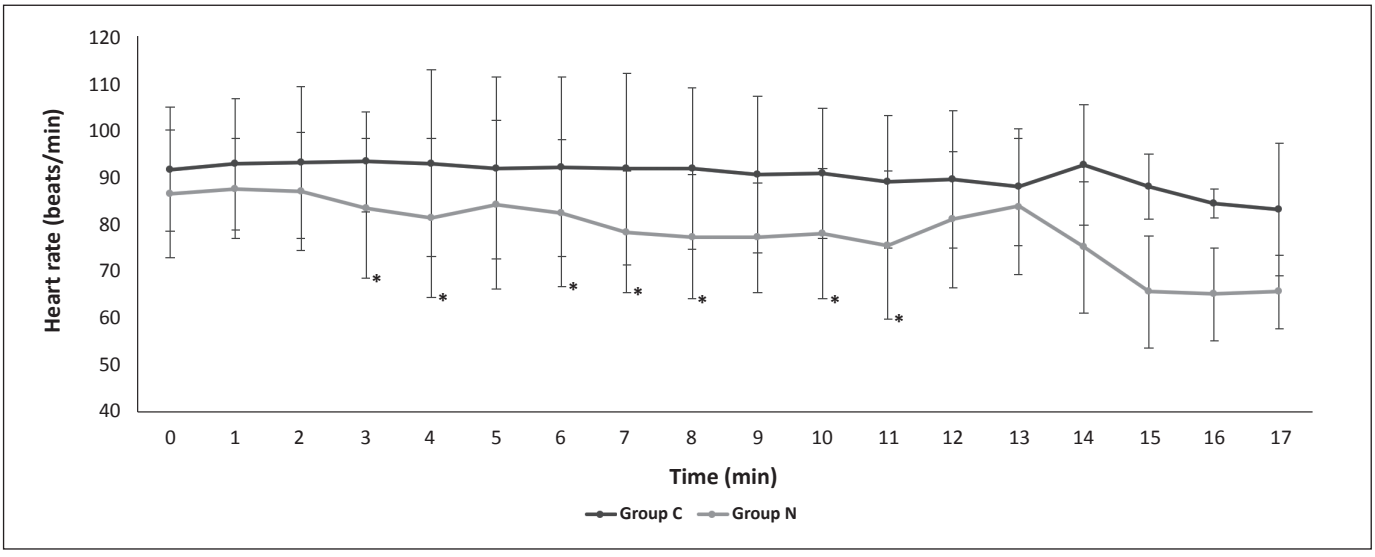

Figure 4. Changes in heart rate before delivery. Markers are means and error bars are standard deviations. **Group C:** Control group; **Group N:** Norephinephrine group; ***:** p<0.05 compared to Group C.

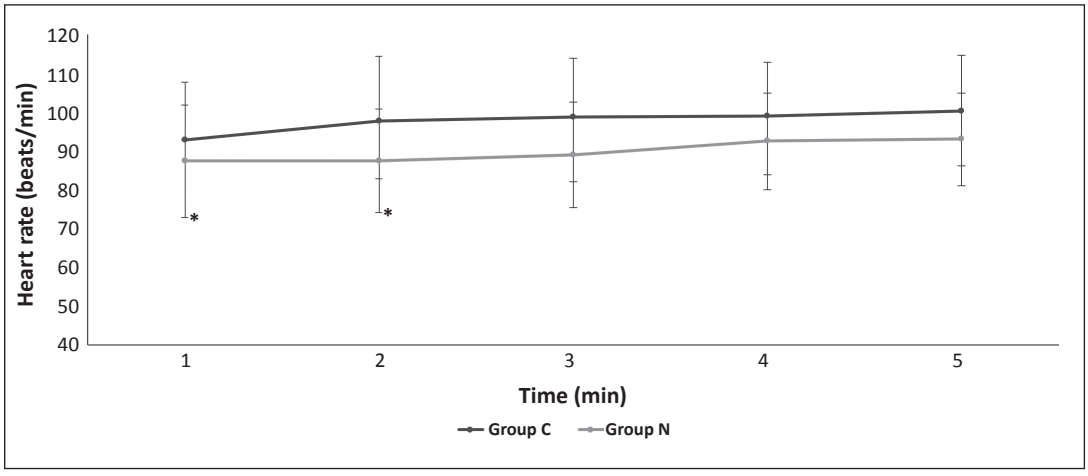

Figure 5. Changes in heart rate after delivery. Markers are means and error bars are standard deviations. **Group C:** Control group; **Group N:** Norephinephrine group; ***:** p<0.05 compared to Group C.

Table III. Perioperative Characteristics

	Control group n=79	Norephinephrine group n=32	p
Postspinal hypotension before delivery	59 (74.7%)	13 (40.6%)	**0.001**
Postspinal hypotension after delivery	24 (30.4%)	10 (32.3%)	0.84
Bradycardia (<50 bpm)	4 (5.1%)	2 (6.5%)	1.00
Nausea	29 (36.7%)	6 (18.8%)	0.065
Vomiting	6 (7.6%)	1 (3.1%)	0.67
Ephedrine requirements (mg)	13.67±11.02	6.09±8.2	**0.001**

Data are presented n (%) and mean±SD.

study were lower in the control group with a higher incidence of hypotension. However, hypotension due to spinal anesthesia is not the sole determinant of low APGAR scores. The interval between skin incision to delivery and the duration of hypotensive episodes are other possible determinants of APGAR scores (8,9). Anesthesia induction to incision and incision to delivery intervals were not recorded, so they could not be assessed. None of the patients had a hypotension episode lasting longer than two minutes. Although it was reported that prophylactic norepinephrine infusion had a positive effect on APGAR scores, it was observed that it had no effect on the umbilical artery pH values. However, none of the newborns' umbilical pH values were <7.2, it may be a concern that norepinephrine decreases uteroplacental blood flow in cesarean sections (10,11). However, in the present study, which is a relatively small series, the mean umbilical artery pH value of the norepinephrine group was found to be 7.36. Similar results were found with other studies in the literature in that norepinephrine does not impair the umbilical artery pH values, which is an indirect indicator of uteroplacental blood flow (12,13). The effect of the rescue ephedrine boluses are one of the important points that are ignored when evaluating neonatal outcomes in studies like in the current study. Because ephedrine crosses the placenta at a higher rate and causes more fetal acidosis. Although we found better neonatal outcomes in the norepinephrine group compared to the control group, the use of ephedrine as a rescue vasopressor in the norephinephrine group can be considered as a limitation of our study (14,15).

Norepinephrine has α-adrenergic receptor activity and weak β-adrenergic receptor agonist activity; therefore, it may be an appropriate vasopressor option to protect maternal blood pressure with less adverse effects on HR and cardiac output (5,16). Prophylactic norepinephrine was found to be more efficient in preventing postspinal hypotension in the literature compared to ephedrine or phenylephrine (17,18). The pure α-agonist effect of phenylephrine is one of the key explanations for the initiation of studies on norepinephrine in obstetric anesthesia; it is known to induce reflex bradycardia and reduced cardiac performance due to stimulation of baroreceptors (19,20). A potential benefit of norepinephrine over phenylephrine is that it does not cause maternal bradycardia (5,21). We observed no difference in the bradycardia incidence between the groups, but there was a significant difference in HR values. We may assume that the prophylactic use of norepinephrine lowers HR, but this decrease is above the bradycardia limit and within the safe zone.

Nausea and vomiting are common after cesarean sections under spinal anesthesia. The use of prophylactic vasopressors during cesarean section significantly reduces the frequency of intraoperative nausea and vomiting (22). There was no difference between the groups in terms of nausea and vomiting, even though the frequency of nausea appeared to be lower in the norepinephrine group. Ali Elnabtity et al. reported that there was no statistically significant difference in the incidence of nausea and vomiting between their norepinephrine and ephedrine groups (18). Nausea was observed in 29 out of 35 pregnant women who developed hypotension. It was thought that brainstem hypoperfusion was the most likely cause of nausea in hypotensive patients. It could be listed the causes of nausea in pregnant women without hypotension as follows: peritoneum or uterus traction emotional causes, ambient odor, oxytocin, ergometrine, ephedrine, and intrathecal fentanyl in conjunction with a local anesthetic in the spinal space.

Phenylephrine is suggested as the first step in the prevention and treatment of postpinal maternal hypotension (23). Since the intravenous form of phenylephrine is not available in our country, ephedrine is used as the first-line vasopressor. Despite the lack of evidence, it is recommended that ephedrine can be used as a second-line vasopressor in conditions where prophylactic norepinephrine is used first (24). Although norepinephrine was used as a prophylactic infusion in our current study, it has another additional feature that administered intermittent bolus as in the use of ephedrine (25). Both norepinephrine and phenylephrine effect α-1 receptors directly. In our study, we used ephedrine as a rescue vasopressor in the norepinephrine group and found that the norepinephrine necessiated used significantly less ephedrine than that of the control group.

Concerns regarding the effects of infusing norepinephrine into peripheral veins have been raised. The vasoconstrictor effect of a diluted 5-6 μg mL^{-1} solution of norepinephrine is seen to be close to that of a 100 μg mL^{-1} solution of phenylephrine, which is widely used around the world, with no increased risk (26). Apart from infusion, 6 μg intermittent boluses of norephinephrine was shown to be effective in preventing spinal-induced hypotension (23). Those who are concerned about using norepinephrine into peripheral veins can administer diluted intermittent boluses. There is no need for a central catheter if phenylephrine and norepinephrine solutions were diluted and infused via a large intravenous cannula (27). Since it is approximately 10 times more diluted than the dose used in intensive care and large peripheral veins are used, there were no peripheral perfusion problems in any of the patients in our research.

The most important limitation of our study is that it is a single-center, retrospective, and small-cohort research. The fact that a prophylaxis group was compared to a group that was not given any prophylaxis may be criticized as a study

design. However, our research will contribute to the literature at a time when more evidence is required to support the widespread use of norepinephrine in obstetrics.

CONCLUSION

Based on retrospective research, we found that prophylactic norepinephrine infusion may minimize the risk of postpinal hypotension during cesarean section, reduce HR without increasing the risk of bradycardia, and improve hemodynamic stability with good fetal and neonatal outcomes. There was a significant reduction in the need for therapeutic ephedrine bolus in pregnant women who received norepinephrine infusion.

We believe that prophylactic norepinephrine infusion is effective in preventing spinal-induced hypotension in cesarean deliveries, but further research is needed as there are not enough studies on the subject in the literature.

AUTHOR CONTRIBUTIONS

Conception or design of the work: SA, SS, GO

Data collection: SA, SS

Data analysis and interpretation: SA, SS, GO

Drafting the article: UK, MEI, OC

Critical revision of the article: UK, MEI, AC

All authors (SA, GO, SS, UK, MEI, AC) reviewed the results and approved the final version of the manuscript.

Conflict of Interest: None

Funding: None

Informed Consent: Retrospective study

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