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The effect of different norepinephrine administration methods on hypotension after spinal anesthesia in caesarean sections

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Abstract

We aimed to evaluate the effect of different routes of norepinephrine (NE) administration on maternal hypotension in pregnant females undergoing spinal anesthesia for caesarean section. 208 pregnant women were divided randomly into 4 groups (n=52). Bolus 4 µg/ml NE was administered intravenous (iv) immediately after spinal anesthesia in Group PB (Prophylactic Bolus). In Group PI (Prophylactic Infusion), 1 ml of saline solution was applied promptly after spinal anesthesia and then the NE infusion was started at 1 ml/min. In Group TB (Treatment Bolus), 1 ml Physiological Saline (PS) was administered after 1 ml/min infusion of PS immediately after spinal anesthesia and then 1 ml/min NE bolus when blood pressure decreased by 20% after the entry. In Group TBI (Treatment Bolus Infusion), 1 ml PS was administered after 1 ml/min infusion of PS immediately after spinal anesthesia, 1 ml NE and then 1 ml/min NE infusion was initiated when blood pressure decreased by 20% after the entry. At the 4th, 6th, and 8th minutes, the PI Group exhibited higher systolic and mean blood pressures than the other groups (p<.001). Additionally, hypotension was statistically lower in the PI Group than in PB, TB, TBI groups (p<.001), and episodes of hypotension, ephedrine required and extra NE boluses given were statistically lower in the PI Group than in the other groups (p<.001). Umbilical vein (UV) pH values were lower in the TBI Group at compared to the other groups (p<.001). It is suggested that a prophylactic infusion of 4 µg/min of NE in the prevention of hypotension following spinal anesthesia for cesarean section will reduce the possibility of maternal hypotension and better maintain fetal well-being than a prophylactic bolus, a treatment bolus or a post-treatment bolus infusion at the same dose.

Keywords: Caesarean, post spinal hypotension, norepinephrine, obstetric anesthesia, spinal anesthesia

Introduction

Although spinal anesthesia is preferred in caesarean sections, there is a high probability of developing hypotension following the procedure. Decreased cardiac output and systemic vascular resistance occurring secondarily to the sympathetic blockade induced by spinal anesthesia are held responsible for the formation mechanism [1].

Hypotension causes nausea, vomiting, dizziness in the mother, bringing the risk of acidosis and neurological changes in the infant. Using vasopressors such as ephedrine, phenylephrine and norepinephrine (NE), as well as intravenous (iv) fluids, is the first option in the current management of maternal hypotension [2-4].

Although ephedrine has been preferred for years, its undesirable effects (e.g., fetal acidosis in high doses and late onset of action) limit its use [5]. Phenylephrine, which passes through the placenta at very low rates, and for this reason, does not cause negative changes in fetal blood gases, is a pure α-agonist agent [5]. For this reason, it must be used with caution in pregnant women who have low heart rates and cardiac outputs [6]. NE, which is an α receptor agonist and a weak β receptor agonist similar to phenylephrine, has entered obstetric anesthesia practice [4]. Theoretically, it reduces heart rates and cardiac output less.

NE can be employed as a prophylactic bolus, infusion, or as a bolus dose, and infusion in the treatment during caesarean

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sections. It has not been elucidated adequately which of the NE administration methods is more effective. The primary objective of the this study was to determine which of the different application methods of NE is more effective in preventing maternal hypotension, and the secondary purpose was to assess its effects on fetal acid-base balance and side effects in pregnants where caesarean delivery is planned under spinal anesthesia.

Material and Methods

Protocol

This study was performed with the clinical research number NCT04951167 after approval from the Malatya Clinical Trials Ethics Committee with protocol code: 2021/120. In addition patients were informed in writing and verbally and their consent was obtained.

Inclusion Criteria

A total of 208 pregnant women over the age of 18 years with ASA (American Society of Anesthesiologists) physical status II, body weight between 50 and 100 kg, and height 150-180 cm, who were scheduled for elective caesarean section under spinal anesthesia were included in the study.

Exclusion Criteria

The pregnant women with cardiovascular or cerebrovascular disease, history of diabetes, hypertension or pregnancy-induced hypertension, renal insufficiency, with known fetal abnormalities, allergy or hypersensitivity to NE, using monoamine oxidase inhibitor, tricyclic antidepressants and those who refused to participate in the study, history of thrombosis in the mesenteric or peripheral vessels were excluded from the study.

Randomization and Blinding

Pregnant females were randomly divided into 4 groups using the sealed envelope method. The person who prepared the study medication and supervised the study was unknown and blind to the study.

Preoperative Procedures

After administering standard aspiration prophylaxis and monitoring hemodynamics, we inserted a peripheral vascular line with an 18G catheter and initiated lactated Ringer's solution at 1ml/kg/hour. We measured basal systolic arterial pressure (SAP) and heart rate (HR) values every 2 minutes and determined them by averaging 3 values.

Anesthesia Management

During spinal anesthesia, 2-2.2 ml of heavy bupivacaine and 15 µg of fentanyl were administered via the L3-4 or L4-5 interval using a 25 G Quincke spinal needle. Following the procedure, the pregnant women was turned supine and rapidly fluid resuscitated with a pillow under the right hip (tilted 30° to the left) and a maximum 1 L Ringer Lactate pump. The liquid rate was then discounted again to 1 ml/kg/h. NE was prepared at 4 µg/ml for the study.

Immediately after spinal anesthesia, an iv bolus of 4 µg NE was administered in Group PB (Prophylactic Bolus) (n=52), and then PS infusion was initiated at 1 ml/min In Group PI (Prophylactic Infusion) (n=52), 1 ml of PS was given at a rate after spinal anesthesia and the trial drug was initiated at 4µg/min. In Group TB (Treatment Bolus) (n=52), 1 ml PS after 1 ml/min. infusion of PS was initiated immediately after spinal anesthesia, and when blood pressure decreased by 20%, 1 ml study solution and then 1 ml/min PS infusion was initiated.

In Group TBI (Treatment Bolus Infusion) (n=52), 1 ml PS was administered after 1 ml/min infusion of PS immediately after spinal anesthesia, 1 ml study solution, and then 1 ml/min study solution infusion was initiated when blood pressure decreased by 20% after the basal.

Heart rate, blood pressure and peripheral oxygen saturation were recorded every 2 mins from intrathecal drug application until delivery. A decrease in SAP of more than 20% from baseline was regarded as hypotension and an additional 4 µg/ml of NE was given in all groups. If it persisted at the next measurement, the second dose of 4 µg NE was administered. Hypotension that did not improve despite two measurements was treated with an intravenous bolus of 10 mg ephedrine. Hypotension of 40% or more was considered severe and treated with 15 mg ephedrine. Bradycardia was defined as a fall in HR to 50 beats/min and was treated with 0.5 mg atropine. Hypertension was accepted as a 20% increase in SAP from baseline and treated with an intravenous bolus of 0.1 mg nitroglycerin. The trial protocol was stopped after delivery of the fetus, but the anesthetist maintained a bolus of NE to treat hypotension. The frequency of episodes of hypotension and hypertension, bradycardia, nausea-vomiting, tremor, sensory block level, Apgar score, umbilical vein (UV) levels, time from intrathecal injection to delivery, incision-delivery time, and uterine incision-delivery time were all documented.

Sample Size

In the power analysis for the present study, given that (α) 0.05, (1-β) 0.80, it was calculated that a total of 208 patients (at least 52 patients for each group) should be included in the study for the maximum decrease in SAP to be 35%.

Statistical Analysis

The variables used in the study were presented as arithmetic mean±standard deviation and numbers (percentages) following the levels of measurement. The Shapiro-Wilk test was used to assess whether numerical variables conformed to the normal distribution. If the assumption of normal distribution was made, the one-way analysis of variance was used to test whether there was a difference between more than two independent groups with respect to numerical variables. After the One-Way Analysis of Variance, multiple comparisons were made with the Tukey Test. When the normal distribution assumption was not met, whether there was a difference between more than two independent groups in terms of numerical variables was examined with the Kruskal-Wallis Analysis of Variance. After the Kruskal-Wallis Analysis of Variance, multiple comparisons were made

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with the Mann-Whitney U Test with Bonferroni Correction. The Pearson Chi-Square Test was used to examine whether there were differences between independent groups in terms of qualitative variables. Whether there were statistically significant differences between the time-dependent measurements with more than two repetitions was examined with the analysis of variance in repeated measurements. Multiple comparisons after analysis of variance in repeated measurements were performed with Bonferroni-Corrected Dependent Samples t-test. In the analyses, $p \leq 0.05$ was accepted as the statistical significance level and the IBM SPSS Statistics 26.0 package program was used for analysis.

Results

A total of 220 pregnant women were to be enrolled. However, 5 pregnants refused spinal anesthesia, 7 pregnants did not satisfy the inclusion criteria, and pregnant women 208 who satisfied the inclusion criteria, being over 18 years of age, ASA II, and undergoing elective caesarean section, were allocated to 4 groups with 52 patients in each group (Figure 1).

There were no statistically significant differences in demographics and time from intrathecal injection to delivery, incision-delivery time, and uterine incision-delivery time co- hydration volume, sensory level among the groups (Table 1).

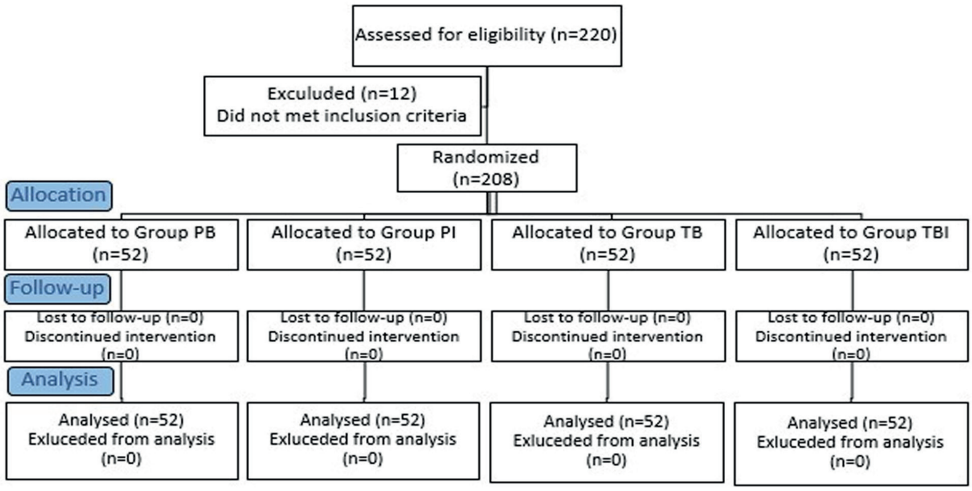

Figure 1. Flow chart of the study

Table 1. The demographic and delivery data (Mean±SD or number)

	TB	TBI	PI	PB	P
Age (years)	30.88±4.6	30.33±5.2	30.60±5.8	30.69±6.6	0.967
Weight (kg)	81.12±11.0	77.21±12.2	77.31±11.4	76.62± 11.0	0.173
Height (cm)	162.82±4.9	160.96±5.7	161.88±4.4	161.07± 5.0	0.216
BKI (kg/m²)	30.54±3.7	29.77±4.2	29.55±4.3	29.60±4.1	0.590
Pregnancy week	38.09±0.7	38.37±0.8	37.99±0.8	38.28±0.9	0.100
Induction-birth duration (min)	10.55±0.5	10.67±0.4	10.44±0.5	10.50±0.5	0.108
Incision-birth duration (min)	4.53±1.0	4.21±0.9	4.44±1.0	4.19±0.8	0.200
Uterine incision-birth duration (min)	2.15±1.0	1.96±1.0	2.04±1.0	2.17±1.1	0.719
Co-hydration volume (mL)	869.23±44.4	848.08 ±50.4	847.12±46.8	850.96±46.9	0.060
Block dermatome					
T4	23 (44.2)	25 (48.1)	23 (44.2)	24 (46.2)	0.975
T5	29 (55.8)	27 (51.9)	29 (55.8)	28 (53.8)	

BMI: body mass index, TB: treatment bolus, TBI: treatment bolus infusion, PI: prophylactic infusion, PB: prophylactic bolus

SAP was statistically and significantly elevated in the PI Group at the 4th, 6th, and 8th min in comparasion with the other groups ($p<.001$). SAP values were similar in TBI and PI Groups at 10 and 12 minutes (Figure 2). It was also found that SAP was statistically similar between groups in other observation periods (Figure 2).

Mean arterial pressure (MAP) was statistically elevated in the PI Group at 4th, 6th, and 8th min compare with the other groups ($p<.001$). MAP values were similar in TBI and PI Groups at 10 min. MAP was found to be significantly elevated in the TBI Group at the 12th minute when compare with the PB Group. No statistical differences were detected between the MAP groups in the other observation periods (Figure 3).

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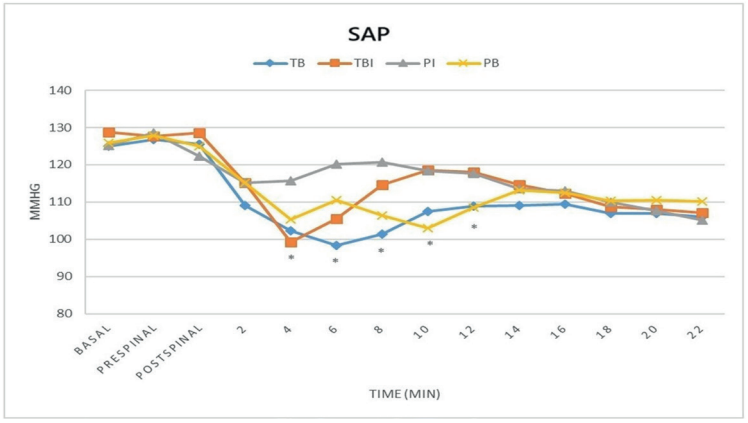

Figure 2. The SBP values of the groups; *=p<0.05 statistically significant in the PI group when compared to the other groups; TB: treatment bolus, TBI: treatment bolus infusion, PI: prophylactic infusion, PB: prophylactic bolus

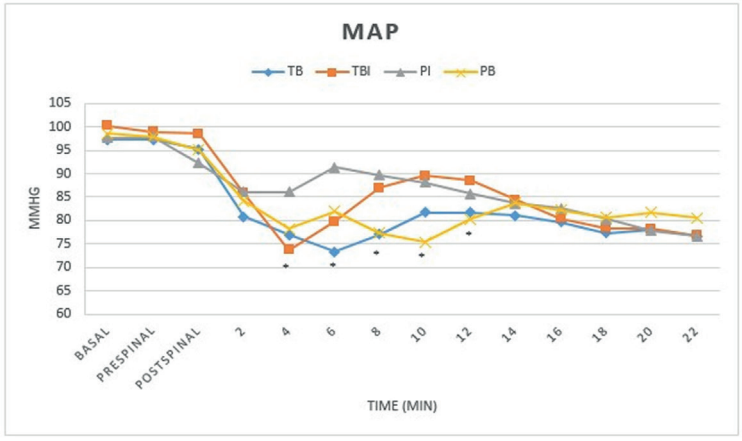

Figure 3. MAP values of the groups; *=p<0.05 statistically significant in the PI group compared to the other groups; TB: treatment bolus, TBI: treatment bolus infusion, PI: prophylactic infusion, PB: prophylactic bolus

Although hypotension was observed in all patients in the TB and TBI Groups, it was significantly lower in the PI Group in comparison with the other groups (p<.001) (Table 2).

The incidence of severe hypotension was higher in the TB, TBI, and PB groups than in the PI Group (p<.001) (Table 2). The number of episodes of hypotension, ephedrine requirement, and NE extra bolus number was statistically lower in the PI Group compared to the other groups (p<.001) (Table 2). The time to the first extra bolus of NE and atropine requirement were statistically similar between groups (Table 2).

HR was significantly lower in the PI Group at the 2nd and 4th minutes when compared to the TB Group, at the 18th minute when compared to the TBI Group, and at the 20th and 22nd minutes compare with all other groups (p<.001) (Figure 4).

Table 2. Hemodynamic parameters

	TB	TBI	PI	PB	p
Hypotension	52 (100)	52 (100)	12 (23.1)	42 (80.8)	**<0.001**
Severe hypotension	15 (28.8)	12 (23.1)	1 (1.9)	6 (11.5)	**0.001**
Hypotension attack count	2.02±0.8[a]	1.75±0.8[b]	0.37±0.7[a.b.c]	1.71±1.3[c]	**<0.001**
Ephedrine requirement	14 (26.9)	13 (25.0)	1 (1.9)	7 (13.5)	**0.002**
Time to first extra bolus (min)	2.83±1.8	2.71±1.7	2.00±0.0	3.28±2.0	0.216
Extra bolus count	1.02±0.[a]	0.75±0.8[b]	0.13±0.3[a.b.c]	0.90±1.1[c]	**<0.001**
Atropine requirement	3 (5.8)	5 (9.6)	1 (1.9)	2 (3.8)	0.419

The same upper-case letters indicate groups with significant differences; TB: treatment bolus, TBI: treatment bolus infusion, PI: prophylactic infusion, PB: prophylactic bolus

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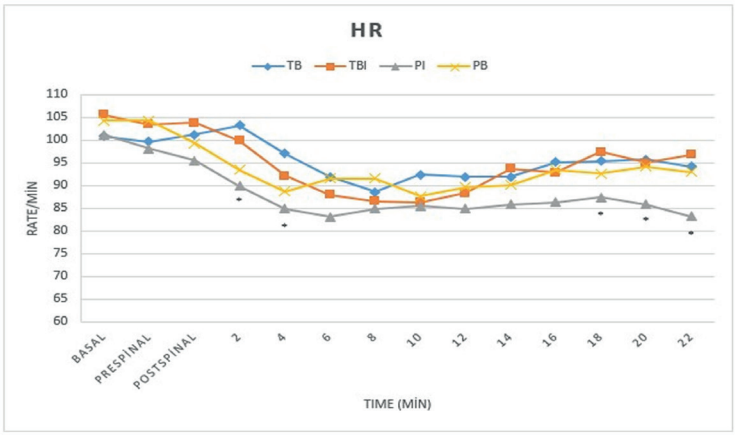

Figure 4. The HR values of the groups; *=p<0.05 statistically significant in the PI group when compared to the other groups; TB: treatment bolus, TBI: treatment bolus infusion, PI: prophylactic infusion, PB: prophylactic bolus

Hypertensive patients were statistically higher in TBI than in other groups (p=0.004) (Table 3).

Nausea rates were statistically lower in PI group, compared to other groups (p<.001) (Table 3). Although vomiting was not detected in TBI and PI groups, it was significantly higher in the PB group (p=0.018) (Table 3). The number of patients with bradycardia, tachycardia, and tremor was similar between the groups (Table 3).

Table 3. Advers effects

	TB	TBI	PI	PB	p
Bradycardia	3 (5.8)	5 (9.6)	1 (1.9)	3 (5.8)	0.461
Tachycardia	42 (80.8)	39 (75)	32 (61.5)	37 (71.2)	0.167
Hypertension	1 (1.9)	6 (11.5)	0 (0)	0 (0)	**0.004***
Tremor	2 (3.8)	0 (0)	0 (0)	0 (0)	0.246
Nausea	29 (55.8)	31 (59.6)	5 (9.6)	24 (46.2)	**<0.001***
Vomiting	2 (3.8)	0 (0)	0 (0)	5 (9.6)	**0.018***

TB: treatment bolus, TBI: treatment bolus infusion, PI: prophylactic infusion, PB: prophylactic bolus

UV pH values were significantly lower in the TBI Group when compared to the other groups (p<.001) (Table 4). UV Partial pressure of carbon dioxide (PCO_2) values were statistically lower in the PI group, compared to the other groups (p=0.005) (Table 4). UV Partial oxygen pressure (PO_2) values were similar between the TB and TBI groups and were significantly lower than the PI and PB groups (p<0.005) (p=0.014) (Table 4). Statistically lower values were found in the UV bicarbonate (HCO_3) values in the TBI Group when compared to the TB Group (p<0.005) (p=0.001) (Table 4). UV Base Excess (BE) was statistically and significantly higher in the TB group, in comparison with the other groups (p<0.005)(p=0.002) (Table 4).

Apgar 1st and 5th min data were similar between the groups (Table 4).

No statistical differences were detected between the groups in terms of the SPO_2 values.

Table 4. Fetal well-being evaluation

	TB	TBI	PI	PB	p
UV pH	7.36±0.05^{a}	7.33±0.05^{a,b}	7.36±0.04^{b}	7.34±0.04	**<0.001**
UV PCO_2	37.77±6.6^{a}	37.17±7.2^{b}	33.99±4.0^{a,b}	35.80±4.3	**0.005**
UV PO_2	23.99±6.8	23.31±6.6^{a}	26.63±5.1^{a}	26.17±5.8	**0.014**
Vein HCO_3	19.88±1.7^{a}	18.35±2.0^{a}	19.06±1.8	19.07±1.9	**0.001**
Vein BE	-4.19±2.4^{a,b,c}	-5.95±2.9^{a}	-5.69±2.4^{b}	-5.50±2.1^{c}	**0.002**
Apgar 1st min	8.63±0.6	8.71±0.7	8.94±0.5	8.75±0.5	0.068
Apgar 5th min	9.96±0.1	9.92±0.2	10.00±0.0	10.00±0.0	0.056

The same upper-case letters indicate groups with significant differences; UV: umbilical vein, PCO_2: partial pressure of carbon dioxide, PO_2: partial oxygen pressure, BE: base excess, TB: treatment bolus, TBI: treatment bolus infusion, PI: prophylactic infusion, PB: prophylactic bolus

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Discussion

In the present study, in which prophylactic NE was applied at 4 µg bolus, prophylactic 4 µg/min infusion, treatment bolus and treatment bolus and infusion administration at the same doses, it was found that prophylactic infusion was superior to other methods in prevention maternal hypotension after spinal anesthesia in caesarean sections.

If post spinal hypotension develops, it may not be possible to maintain blood pressure using physiologic methods, and this rate can be as high as 68.42% when no prophylactic measure is used [7]. When NE was first used by Ngan Kee et al. [8] by computer-controlled infusion, it was shown that although its effect on blood pressure was similar to phenylephrine, the heart rate and cardiac output of patients were higher with norepinephrine.

Vallejo et al. [9] used phenylephrine 6 µg/kg/h or norepinephrine 3 µg/kg/h to prevent hypotension in spinal anesthesia in elective caesarean sections and reported that the need for additional bolus dose agents was similar. They suggested that norepinephrine may be an alternative agent. Both NE and Ephedrine infusion is effective in keeping maternal SAP between 80% and 120% of baseline [10]. Ngan Kee et al. [11] initiated a 2.5 µg/min infusion of NE, which they prepared as 5 µg/ml in patients where caesarean delivery was scheduled. They administered bolus 5 µg NE to the NE bolus group and titrated NE manually, and similar to our study, they found that the incidence of hypotension was lower in the prophylactic infusion group. They reported the incidence of hypotension was 17% in the prophylactic infusion group. Chen et al. [4] investigated the safety and efficacy of prophylactic NE infusion in three different groups at a dose of 5, 10, and 15 µg/kg/h. In their preliminary study, it was found that 2.5 µg/kg/hr could not maintain blood pressure, and a minimum dose of 5 µg/kg/h was required to effectively treat hypotension. Five µg/kg/h NE infusion significantly reduced the incidence of hypotension when compared to the control group. It was reported that patients in the group treated with high-dose NE (15 µg/kg/h) infusion experienced more hypertension attacks. As a result, they reported that 5-10 µg/kg/h NE infusion was appropriate to maintain blood pressure in caesarean sections. Also, Hasanin et al. [12] reported that prophylactic doses of 0.05 and 0.075 µg/kg/min effectively reduced post spinal hypotension, which supports the result of our study.

In this study, the reason why the incidence of hypotension development, the possibility of severe hypotension, and the need for ephedrine and extra bolus NE was low in the PI Group may be because NE was administered prophylactically. Although the effect of NE starts quickly, it peaks within 1-2 minutes and the effect lasts for 2-10 minutes in bolus applications. The infusion of NE may have been effective in maintaining a certain plasma level of the drug because infusion is recommended for all drugs with a short duration of action. Maintaining an effective plasma level may be responsible for keeping maternal hemodynamics more stable. For this reason, prophylactic infusion of vasopressor agents was recommended in patients scheduled for cesarean delivery with spinal anesthesia in the recently published guidelines [2-13]. The time needed for the onset of the drug's duration of action in bolus applications for therapeutic purposes after hypotension develops may have been effective in increasing the number of hypotension attacks.

Kee et al. [14] found elevated HR values and decreased hemodynamic stability after ephedrine infusion. Ngan Kee et al. [11] reported that although the mean HR was lower in patients receiving NE by infusion, the number of patients who had CAD episodes <60 beats/min was low and similar between groups. For this reason, we think that the lower HR values in the PI Group compared to the other groups occurred because of the lower ephedrine requirement in this group.

Autoregulation mechanisms are ineffective in maintaining uteroplacental blood flow, and the provision of uteroplacental blood flow is directly proportional to maternal blood pressure. As uterine vascular resistance increases, uteroplacental blood flow decreases [15]. Depending on the severity of maternal hypotension, undesirable disorders may occur in the infant [16].

While it was found that blood acid-base balance was better preserved in the infants of mothers who received NE [10], Minzter et al. [17] found that NE did not adversely affect the blood flow from the mother to the fetus.

Uteroplacental perfusion is very important in maintaining fetal well-being and stable maternal blood pressure is an important factor in perfusion. More unstable blood pressures in the group that received bolus and subsequent infusion NE infusion may indirectly be the cause of low UV blood pH. Because the duration and degree of hypotension are important factors determining the fetal acid-base balance and fetal acidosis.

Although uterine artery (UA) blood gas values show direct results in determining fetal well-being, UV blood gas values indirectly provide information about the condition of the fetus and placenta [7]. In the present study, the inability to study UA blood gas values due to the facilities of our clinic was one of the limitation criteria of our study.

Conclusion

In conclusion; in the present study, where NE was applied with direct α1 and limited β2 activity with different methods in caesarean sections, we believe that prophylactic infusion of NE is superior to prophylactic bolus or therapeutic applications of NE in preventing maternal hypotension. We also detected prophylactic bolus NE administration resulted in better fetal well-being.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The present study was conducted with clinical trial number: NCT04951167 after obtaining the approval from Malatya Clinical Research Ethics Committee with the protocol code 2021/120.

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