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Original Article

Effect of norepinephrine and phenylephrine on maternal hemodynamic changes after spinal anesthesia in cesarean section: A randomized clinical trial

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Abstract

Background: Hypotension after spinal anesthesia is a serious complication during cesarean sections, potentially reducing maternal cardiac output and placental blood flow, affecting both mother and baby. This study aimed to compare the effects of norepinephrine and phenylephrine on maternal hemodynamic changes following spinal anesthesia in elective cesarean surgeries.

Methods: In this clinical trial study, 52 pregnant mothers' candidates for elective cesarean surgery were divided into two groups. After spinal anesthesia, the norepinephrine group received a 10-microgram bolus of norepinephrine, while the phenylephrine group received 100 micrograms of phenylephrine. The primary outcomes included blood pressure, heart rate, and measurement time. These were recorded three times before the start of spinal anesthesia, immediately after, and every 3 minutes until discharge, and then twice at 3-minute intervals after childbirth.

Results: Mean arterial pressure in norepinephrine group was always higher than phenylephrine. Their difference was significant at the ninth minute ($p<0.001$) and the twelfth minute ($P=0.009$). Diastolic pressure in the two studied groups was significant at the ninth minute ($p<0.001$). 2 patients in norepinephrine group (7.6%) and 6 (23%)patients in phenylephrine group needed vasopressor. 3.8% of patients in norepinephrine group and 34% of patients in phenylephrine group had bradycardia ($P=0.020$).

Conclusion: This study shows that norepinephrine is as effective as phenylephrine in preventing blood pressure drop in patients undergoing cesarean section, but it does not cause bradycardia.

Keywords: Norepinephrine, phenylephrine, spinal anesthesia, cesarean surgery.

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Cesarean section is one of the most common surgeries among women. Therefore, it is important to choose a low-risk and favorable anesthesia technique for the mother and the children (1). Choosing the type of anesthesia for cesarean depends on the surgical indication, urgency and the patient's desire. The chosen method of anesthesia for cesarean delivery is spinal anesthesia (2). The main complications of this method include: the difficulty of controlling the level of anesthesia, hypotension (45-100%), nausea and vomiting, bradycardia, dysrhythmia, and post-operative headache (3). The varying reports of hypotension incidence across different studies are likely due to differences in the definition of hypotension and the volume of prehydration used (2, 4, 5). Since uterine blood flow does not have autoregulation. Hypotension of the mother, especially if the systolic blood pressure is below 90 mm Hg, causes a decrease in blood supply to the placenta and asphyxia of the baby (6).

Treatment methods for hypotension include shifting the uterus to the left, administering oxygen, lowering the head of the bed, and using intravenous fluids or medications such as ephedrine, phenylephrine, and norepinephrine (7). Although the usefulness of phenylephrine has been proven in the treatment of hypotension following spinal anesthesia, there are differences of opinion in recent studies regarding the selectivity of this drug (8-10). Norepinephrine is used in the treatment of hypotension by increasing the tone of vascular smooth muscles and is also used in cardiopulmonary resuscitation. Although prophylactic injection is recommended to prevent blood pressure drop caused by spinal anesthesia, intravenous bolus injection is still the drug pattern preferred by most anesthesiologists. In addition, the use of intermittent intravenous norepinephrine boluses to prevent hypotension induced by spinal anesthesia in patients undergoing cesarean delivery appears to be feasible without apparent side effects (10, 7). Given the lack of a standard protocol and concerns about bradycardia caused by phenylephrine, this study aimed to directly compare the effects of norepinephrine and phenylephrine on maternal hemodynamic changes after spinal anesthesia in cesarean section, this study aimed to compare the effects of norepinephrine and phenylephrine on maternal hemodynamic changes following spinal anesthesia during cesarean section.

Methods

Study design: This study, with the ethics code IR.MUBABOL.REC.1401.026 and clinical trial registry code IRCT20101213005381N15 was a blind randomized clinical trial. It was conducted on pregnant women scheduled for elective cesarean surgery at Ayatollah Rouhani Hospital, affiliated with Babol University of Medical Sciences, during 2021-2022. The sample size was calculated using G*Power software. With $\eta^2 = 0.05$, a type I error rate of 0.05, 80% power, and two groups measured six times, the required sample size was 22 participants per group. Accounting for a 20% dropout rate, the final sample size was set at 52 participants.

Participants: The study sample consisted of 52 pregnant women aged 18-45 who were candidates for elective caesarean section under spinal anesthesia. Inclusion criteria included: ASA Class I or II (American Society of Anesthesiology), elective caesarean section, absence of underlying hypertension, and no use of blood pressure-regulating medications. Exclusion criteria included: excessive sweating during surgery, surgeries lasting longer than 3 hours, and the need for general anesthesia during the procedure. The sampling method employed in this study was random. Random allocation was performed using permuted blocks of size 4, which comprised random combinations of 2 to A (phenylephrine) and 2 to B (norepinephrine). A statistician created the random sequence within the blocks. This study was single-blind: patients were unaware of the drug regimen, whereas the anesthesiologist and the patient assessor (anesthetist assistant) were informed of it.

Interventions: Following the mother's admission, necessary explanations regarding the plan and procedure were provided in the waiting room, and written informed consent was obtained. An 18-gauge angiocatheter was utilized, and 500 mL of Ringer's solution was administered. The pregnant woman was then taken to the operating room and transferred to the surgical bed. A blood pressure cuff was placed on the right arm, and a pulse oximeter probe was attached to the index or middle finger of the left hand. In a sitting position, after disinfecting the area in a sterile manner, 12 mg of Marcaine was injected into the midline of the L4-L5 or L5-S1 intervertebral space using a 25-gauge Quinque spinal needle. In the norepinephrine group, 10 micrograms of norepinephrine were injected, while in the phenylephrine group, 100 micrograms of phenylephrine were administered. During the operation, if there was a drop in mean arterial pressure exceeding 20% of baseline or a decrease in systolic pressure below 90 mmHg, 10 micrograms of norepinephrine were injected into the norepinephrine group, and 100 micrograms of phenylephrine were injected into the phenylephrine group. Additionally, if the heart rate dropped below 60 beats per minute, 0.6 mg of atropine was administered in both groups.

Outcomes: The primary outcomes included systolic, diastolic, and mean blood pressure, along with heart rate, measured three times before the start of spinal anesthesia, immediately after the start of spinal anesthesia, every 3 minutes until delivery, and twice at 3-minute intervals after delivery. The secondary outcome was the newborn's Apgar score, measured at 1 and 5 minutes.

Statistical analysis: Statistical analyses were performed using SPSS Version 22 software. Descriptive statistics were presented as means and standard deviations for quantitative data and as frequencies and percentages for qualitative data. Baseline characteristics of the groups were compared using an independent t-test for continuous variables and Fisher's Exact Test for categorical variables. Repeated-measures analysis was used to compare trends in hemodynamic variables (mean arterial pressure, systolic blood pressure, diastolic blood pressure, and heart rate) between the two groups over time. This test accounted for intra-group

(within-subject) and inter-group (between-subject) effects, as well as the interaction between time and group. Mauchly's test was used to assess the assumption of sphericity, and Greenhouse-Geisser corrections were applied when necessary. The Apgar scores at the first and fifth minutes were compared between groups using Fisher's Exact Test. Statistical significance was set at $p<0.05$.

Results

The current study is a randomized, single-blind clinical trial conducted in 52 pregnant women who were candidates for elective cesarean surgery (Figure 1). Among all the women who were investigated, only 1 (1.92%) person had a history of gestational diabetes but was not taking any medicine. In this study, 23 (44.24%) people had two children, 11 (21.15%) had one child, and 18 (34.61%) had more than two children. The number of parities was 1 in 18 (34.61%) individuals, 2 or more in 22 (42.31%), and 0 in 12 (23.08%). The average age of pregnant women in the two drug groups, phenylephrine and norepinephrine, was compared (Table 1), and the results showed that the two groups were similar in average age, with no significant difference (P=0.597). In pregnant women under investigation, hemodynamic variables, including mean arterial pressure, diastolic blood pressure, systolic blood pressure, and heart rate before the start of anesthesia, were measured three times, and the average was reported as the baseline value (Table 1), which means the difference was not significant.

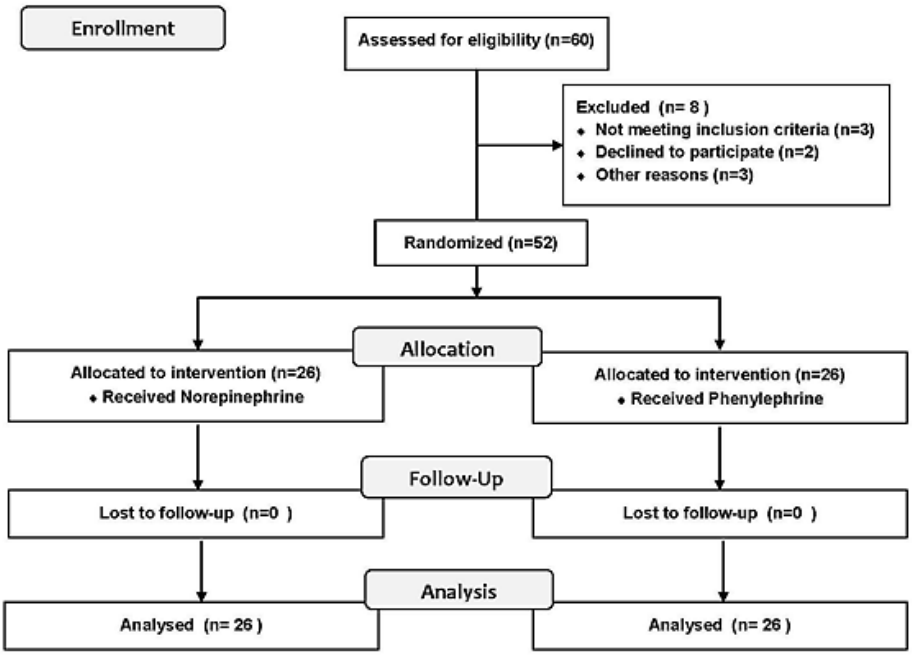

Figure 1. Flow chart of the study participants

Intergroup comparison of mean arterial pressure (Table 2) indicated that, although the mean arterial pressure in women receiving norepinephrine was consistently higher at all measurement times except during drug injection and the second measurement after delivery, the differences were significant only at the 9th ($p<0.001$) and 12th (P=0.009) minutes following the onset of anesthesia. The results of repeated measures demonstrated that the effect of norepinephrine on mean arterial pressure changes was significantly different from that of phenylephrine (P=0.020). In women receiving phenylephrine, these changes exhibited a decreasing trend until the ninth minute, followed by a relative increase until the twelfth minute. In the last measurement before the delivery, its value had decreased relatively. Conversely, the trend of changes in the norepinephrine group showed a relative increase from the first measurement to the twelfth minute after the start of anesthesia, with a decrease of 10 units in the last measurement before the delivery. Ultimately, in the final measurement, the mean arterial pressure of the norepinephrine group was slightly higher than that of the phenylephrine group, although this difference was not significant (P=0.656). The average heart rate of women receiving norepinephrine was consistently higher (Table 2). It is noted that, except the anesthetic injection time and the measurement times after the delivery, in all repeated measurements from the start of anesthesia until the delivery, the heart rate in the norepinephrine group was significantly higher than in the phenylephrine group ($p<0.001$). Furthermore, repeated-measures analysis showed a

significant difference in the effects of norepinephrine and phenylephrine on heart rate trends (p<0.001). In patients receiving norepinephrine, except for the increase observed in the first measurement after the start of anesthesia (third minute), the trend of changes decreased until the last measurement. In contrast, in the phenylephrine group, a decreasing trend was noted until the ninth minute after the start of anesthesia. The Apgar score of the first minute of the newborn was 7 or higher in both groups (Table 3), and according to the results, no significant difference was observed in the Apgar score of the newborns in the two groups. In the fifth minute, it was 9 and above in both groups.

Table 1. Baseline characteristics in norepinephrine and phenylephrine group

Variable	Norepinephrine Mean±SD	Phenylephrine Mean±SD	P-value*
Age	30.23±7.58	31.15±4.55	0.597
Mean Arterial Pressure	92.71±10.29	94.56±7.72	0.464
Diastolic Blood Pressure	77.73±10.42	77.5±8.03	0.929
Systolic Blood Pressure	124.13±9.02	125.28±8.6	0.639
Heart rate	99.36±12.08	98.4±14.16	0.798

* Independent samples t-test

Table 2. Blood pressure and heart rate at different times in norepinephrine and phenylephrine group

Variable		Norepinephrine Mean±SD	Phenylephrine Mean±SD	P-value*
Mean Arterial Pressure				
Time of Anesthesia Drug Injection		85.73±13.29	87.27±11.02	0.625
After Anesthesia Starts	Three Minutes	89.62±19.23	86.38±19.26	0.548
	Six Minutes	90.58±21.78	80.81±15.22	0.067
	Nine Minutes	90.27±19.2	72.92±12.87	<0.001
	Twelve Minutes	90.04±16.06	78.85±13.58	0.009
	Fifteen Minutes	80.65±13.42	77.54±11.79	0.378
After infant delivery	First Measurement	85.77±17.71	83.19±14.29	0.567
	Second Measurement	81.92±13.23	83.73±15.75	0.656
P-value**		0.02		
Diastolic Blood Pressure				
Time of Anesthesia Drug Injection		119.77±11.33	122.08±10.84	0.457
After Anesthesia Starts	Three Minutes	120.88±24.47	117.04±15.98	0.505
	Six Minutes	118.35±20.36	109.54±14.98	0.082
	Nine Minutes	117.35±19.57	99.46±13.72	<0.001
	Twelve Minutes	116.77±20.99	106.12±58.94	0.04
	Fifteen Minutes	110.38±16.91	107.42±9.91	0.445

Variable		Norepinephrine Mean±SD	Phenylephrine Mean±SD	P-value*
After infant delivery	First Measurement	118.38±16.14	116.04±15.65	0.597
	Second Measurement	116.31±13.19	114.85±9.68	0.651
P-value**		0.043		
Systolic Blood Pressure				
Time of Anesthesia Drug Injection		70.42±16.68	71.31±13.35	0.834
After Anesthesia Starts	Three Minutes	70.54±18.63	75.35±15.18	0.313
	Six Minutes	69.92±16.98	67.96±16.15	0.671
	Nine Minutes	75.35±16.74	69.15±14.17	<0.001
	Twelve Minutes	71.58±18.58	64.15±77.79	0.161
	Fifteen Minutes	65.23±15.96	66.42±14.66	0.78
After infant delivery	First Measurement	67.58±14.29	72.42±17.64	0.282
	Second Measurement	69.69±17.17	70.04±20.04	0.947
P-value**		0.488		
Heart Rate				
Time of Anesthesia Drug Injection		98.04±12	97.69±13.65	0.923
After Anesthesia Starts	Three Minutes	109.35±14.07	90.96±15.74	<0.001
	Six Minutes	109.46±12.54	84.08±13.89	<0.001
	Nine Minutes	107.42±13.95	76.19±16.63	<0.001
	Twelve Minutes	103.96±13.13	79.10±77.66	<0.001
	Fifteen Minutes	101.12±13.49	84±14.26	<0.001
After infant delivery	First Measurement	100.96±16.68	94.15±11.87	0.105
	Second Measurement	100.35±12.57	94.96±9.68	0.199
P-value**		<0.001		

* Independent t-test, ** Between group differences (Repeated Measures ANOVA)

Table 3. The level of Apgar score at the first minute in norepinephrine and phenylephrine group

Apgar Group	7-8 Frequency (%)	8-9 Frequency (%)	9-10 Frequency (%)	p-value*
Norepinephrine	1 (3.7)	3 (11.5)	22 (84.8)	0.601
Phenylephrine	2 (7.6)	2 (7.6)	22 (84.8)	

* Fisher's exact test

Discussion

In the present study, the effect of norepinephrine drug on changes in mean arterial pressure and systolic blood pressure was significantly different from phenylephrine drug, so that blood pressure in women receiving norepinephrine was almost always higher, although the difference was only in the ninth and twelfth minutes after anesthesia was significant from the beginning. There was a significant difference in diastolic blood pressure changes between the two study groups only at the ninth minute. These results are comparable with the findings of studies conducted in this field. Studies in this field do not have the same results. Some studies found a significant difference between norepinephrine and phenylephrine in terms of controlling blood pressure and treating hypotension during elective cesarean section, while in other studies, no difference was seen between the two groups in terms of controlling and treating hypotension during cesarean section. For example, in the study by Xu et al. (11), by reviewing three clinical trials, it was concluded that norepinephrine and phenylephrine have no significant difference in the treatment of maternal hypotension in elective cesarean surgery. On the other hand, in the study of J. P. Tiwari et al. (12), it was observed that the need to prescribe a bolus dose to treat hypotension in the norepinephrine group is significantly lower than in the phenylephrine group.

These differences between studies may be related to possible reasons e.g., differences in patient populations and doses. But in terms of mean arterial pressure during surgery, no difference was observed between the two groups. Also, in the study of Warwick et al. (13) it was observed that accurate control of blood pressure in norepinephrine group is more than phenylephrine. Therefore, it seems that the results of the studies are not completely identical, but in general, it is concluded that norepinephrine is better than phenylephrine in terms of intraoperative blood pressure control, as well as in terms of the occurrence of blood pressure complications and the need for dosage. Intraoperative bolus therapy is the same or better. In the present study, the average heart rate in the group receiving norepinephrine was always higher than the group receiving phenylephrine. These results are completely consistent with the findings of studies conducted in this field. In the study of Warwick et al. (13), it was observed that the incidence of bradycardia in the norepinephrine group is significantly lower than in the phenylephrine group. In the systematic review conducted by Shiqin et al. (11), bradycardia was observed significantly less in norepinephrine group than in phenylephrine group. In the study of J. P. Tiwari et al. (12), it was observed that the frequency of bradycardia was higher in the phenylephrine group than in the norepinephrine group, but no difference was observed in terms of the average heart rate between the two groups. In the study of Anna Lee et al. (14) by reviewing 7 clinical trials, it was observed that the incidence of bradycardia is more frequent in the phenylephrine group than in the norepinephrine group.

Therefore, it is concluded that norepinephrine drug provides better control over the heart rate of patients during elective cesarean section than phenylephrine. The results of the present study showed that there was no significant difference between the Apgar scores of infants in the two intervention groups, which is consistent with the results of the study by Dailichen et al. (2018) (15). In addition to the lack of investigation into the safety of norepinephrine administration for the fetus and newborn, other general limitations of the study include the relatively small sample size, which may limit the generalizability of the findings, and the single-center design, which could reduce external validity. These factors should be taken into account when interpreting the results, as they may affect the applicability of the conclusions to broader populations or different clinical settings and may limit our understanding of the potential risks to both mother and fetus.

As a conclusion, the results of the study showed that norepinephrine is as effective as phenylephrine in preventing maternal hypotension, but it provides a more stable hemodynamics condition for mothers under spinal anesthesia in cesarean surgery. However, this study did not evaluate the impact of norepinephrine administration on fetal well-being, a critical aspect that warrants further investigation. Fetal safety must be prioritized alongside maternal health when considering vasoconstrictor use during pregnancy, as certain in utero exposures may lead to adverse outcomes. Future studies should include fetal assessments, such as cord blood analysis, and incorporate fetal hemodynamic monitoring to provide a more comprehensive understanding of the implications of these medications. Incorporating recent research on fetal biomarkers and hemodynamics will contribute to a more rigorous understanding of the risks and benefits associated with vasoconstrictor use in this setting.

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Ethics approval: The study was conducted with approval from the Institutional Ethics Committee (Ref. No.: IR.MUBABOL.REC.1401.026) and the Clinical Trial Registry code IRCT20101213005381N15.

Conflict of interests: The authors declare that there are no financial or non-financial conflicts of interest related to this work.

Authors' contribution: N.B. and M.M. designed the study, F.N. collected data, H.Sh. designed and analyzed data, all authors wrote the manuscript and approved its final version.

Informed consent statement: All subjects that enrolled in this study signed inform consent form.

Data sharing statement: The datasets are available from the corresponding author on reasonable request.

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