

Comparative Effects of Ephedrine and Norepinephrine on Fetal Acid–Base Status during Cesarean Delivery under Spinal Anesthesia: A Randomized Double-Blind Study

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Abstract

Background

Postspinal hypotension during cesarean delivery may compromise uteroplacental perfusion. Ephedrine and norepinephrine are commonly used vasopressors, but comparative evidence regarding their fetal acid–base and maternal hemodynamic effects remains debated. We aimed to compare umbilical arterial blood gas parameters and maternal outcomes following treatment with these agents.

Methods

In this prospective, randomized, double-blind trial, parturients undergoing elective cesarean delivery who required vasopressor treatment for postspinal hypotension (SBP < 80% of baseline) were included in the analysis population. Patients received either 5 µg norepinephrine boluses (n = 52) or 5 mg ephedrine boluses (n = 50). The primary outcome was umbilical arterial (UA) pH. Secondary outcomes included UA pCO₂, base excess, lactate levels, maternal hemodynamic stability, and Apgar scores.

Results

The median umbilical arterial pH was significantly lower in the norepinephrine group compared to the ephedrine group (7.33 [7.29–7.35] versus 7.35 [7.32–7.39]; P = 0.010). However, the incidence of neonatal acidosis, defined as a UA pH < 7.20, was low and did not differ significantly between the norepinephrine and ephedrine groups (4.0% vs. 1.9%; P = 0.614). UA pCO₂ was higher in the norepinephrine group (45.2 [40.4–52.4] mmHg vs. 40.9 [37.5–44.7] mmHg; P = 0.006), while markers of fetal metabolic status, including base excess (P = 0.828) and lactate concentrations (P = 0.733), were equivalent between treatment arms. Apgar scores at 1 and 5 minutes were also comparable (P > 0.05). Incidence of maternal hypotension, reactive hypertension, and bradycardia showed no significant differences (P > 0.05).

Conclusions

Norepinephrine was associated with a statistically lower UA pH than ephedrine; however, both agents maintained parameters within physiological ranges. These results suggest that norepinephrine may serve as a suitable alternative for managing postspinal hypotension, offering comparable maternal stability and fetal safety.

Introduction

Spinal anesthesia is the most commonly preferred anesthetic technique for cesarean delivery because it provides rapid onset of action, produces a reliable sensory block, and reduces the risk of aspiration

associated with general anesthesia.^{1,2} However, the principal drawback of this technique is the development of maternal hypotension resulting from blockade of preganglionic sympathetic nerve fibers.³

Spinal anesthesia–induced hypotension occurs in up to 60–80% of cesarean deliveries and is associated not only with intraoperative nausea, vomiting, and reduced maternal comfort, but also with an acute decrease in uteroplacental blood flow, thereby increasing the risk of fetal hypoxia and acidosis.^{4,5} Accordingly, maintaining maternal hemodynamic stability following spinal anesthesia is of critical importance for both maternal safety and fetal well-being.⁶

Intravenous fluid loading and vasopressor administration constitute the cornerstone strategies for the management of spinal anesthesia–induced hypotension.⁷ Historically, ephedrine has been used as the first-line agent for many years based on the assumption that it preserves uteroplacental blood flow.^{3,8} However, ephedrine readily crosses the placenta and has been associated with increased fetal metabolic activity, leading to lower umbilical arterial (UA) pH values and greater base deficit, which has raised concerns regarding its neonatal metabolic effects.⁹ Although phenylephrine, a pure α -adrenergic agonist, has gained prominence in recent years because of its lower association with fetal acidosis, its potential to induce maternal bradycardia and reduce cardiac output represents a clinically relevant limitation.¹⁰

In this context, norepinephrine has emerged as a promising alternative in contemporary obstetric anesthesia practice.¹¹ Through its potent α -adrenergic effects, norepinephrine maintains vascular tone, while its modest β -adrenergic activity may help preserve heart rate (HR) and cardiac output.¹² Previous studies have demonstrated that norepinephrine stabilizes maternal blood pressure with efficacy comparable to phenylephrine, while being associated with less maternal tachycardia than ephedrine and superior preservation of cardiac output compared with phenylephrine.^{13,14}

Nevertheless, randomized controlled trials directly comparing the effects of norepinephrine and ephedrine on neonatal metabolic status, beyond their efficacy in preventing maternal hypotension, remain limited.^{15,16} In particular, the potential implications of norepinephrine's vasoconstrictive properties for uteroplacental circulation and, ultimately, fetal acid–base balance require further clarification.

Accordingly, we conducted this prospective, randomized, double-blind study to compare the effects of ephedrine and norepinephrine on fetal acid–base status during cesarean delivery under spinal anesthesia. The primary objective was to evaluate fetal acid–base balance, specifically UA pH. Secondary objectives included assessment of maternal hemodynamics, total vasopressor requirements, and neonatal Apgar scores. We hypothesized that norepinephrine and ephedrine would result in comparable fetal acid–base profiles and maternal hemodynamic stability, with both agents maintaining neonatal metabolic status within clinically normal ranges.

Materials and Methods

Study design and participants

This was a prospective, double-blind, randomized controlled trial with a 1:1 allocation ratio comparing ephedrine and norepinephrine in parturients undergoing elective cesarean delivery under spinal anesthesia. The study was conducted at Health Sciences University Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye. Ethical approval was obtained from the Harran University Clinical Research Ethics Committee (approval no. HRÜ/25.08.38; approval date: April 28, 2025), which served as the approving ethics board for this randomized controlled study. Written informed consent was obtained from all participants prior to enrollment. The trial was prospectively registered at ClinicalTrials.gov (Identifier: NCT06921473) on April 1, 2025. The study was designed, conducted, and reported in accordance with the CONSORT 2025 guidelines.

Eligible participants were women aged 18–45 years with healthy, singleton term pregnancies (≥ 37 weeks), classified as American Society of Anesthesiologists physical status I–II, and scheduled for elective cesarean delivery. In this study, elective delivery was defined as a planned procedure in the absence of labor or ruptured membranes, primarily indicated for previous cesarean section, breech presentation, or maternal request.

Exclusion criteria included hypertensive disorders of pregnancy, known systemic disease, multiple gestation, emergency cesarean delivery, contraindications to spinal anesthesia, or known allergy to study medications. To ensure that neonatal acid–base status primarily reflected the pharmacological intervention, we strictly excluded patients with pre-diagnosed fetal growth restriction (FGR) identified via standardized growth curves and pathological Doppler indices suspected fetal distress, oligohydramnios, or any known congenital anomalies.

A total of 180 parturients were screened for eligibility, of whom 155 were randomized. Patients who subsequently developed postspinal hypotension (defined as a $> 20\%$ decrease from baseline systolic blood pressure) requiring vasopressor therapy constituted the analysis population, resulting in a final sample of 102 patients (ephedrine group, $n = 50$; norepinephrine group, $n = 52$). This approach was a methodological necessity, as the pharmacological intervention the administration of either ephedrine or norepinephrine could only be initiated upon the occurrence of the predefined clinical event (hypotension). By focusing on the participants who actually required and received the intervention, the analysis was aligned with the therapeutic objective of comparing the fetal and maternal effects of ephedrine and norepinephrine following the onset of postspinal hypotension.

To ensure procedural consistency and minimize confounding variables, all spinal anesthesia administrations and hemodynamic management were performed by a dedicated team of senior anesthesiologists. Similarly, all surgical procedures were conducted by the same group of senior obstetricians using a standardized surgical technique to maintain a consistent uterine incision-to-

delivery interval. All neonatal assessments and cord blood sampling were performed by a pediatric team blinded to the group assignments.

Randomization and Blinding

Eligible participants were assigned to either the ephedrine or norepinephrine group (1:1 ratio) using a computer-generated block randomization sequence with varying block sizes, created by an independent statistician. Allocation concealment was maintained through sequentially numbered, opaque, sealed envelopes. To ensure clinical relevance and focus on the primary outcome, the final analysis population was predefined as patients who developed postspinal hypotension requiring vasopressor intervention. Accordingly, envelopes were opened in the operating room immediately prior to the initiation of spinal anesthesia once eligibility criteria were confirmed. Because postspinal hypotension could not be predicted before spinal anesthesia, allocation assignment did not influence the occurrence of hypotension or subsequent vasopressor indication, while blinding was maintained throughout the study period.

To ensure a double-blind design, study medications were prepared by an independent investigator not involved in clinical care or data collection. Norepinephrine and ephedrine were provided in visually identical 10 mL syringes containing colorless, indistinguishable solutions. Each milliliter of the solution contained either 5 µg of norepinephrine or 5 mg of ephedrine, diluted with 0.9% normal saline. Syringes were labeled only with the randomization code. Participants, the anesthesiologists administering the spinal block, and the investigators responsible for neonatal assessments and data analysis remained blinded to group assignments throughout the study period.

Sample Size Calculation and Statistical Analysis

An a priori sample size calculation was performed using G*Power (version 3.1.9.6) based on UA pH, which constituted the primary outcome. The calculation was derived from data reported in a randomized controlled trial comparing ephedrine and norepinephrine by Ali Mohamed Ali Elnabtity and Selim (2020).¹⁷ Using the reported mean umbilical cord pH values and standard deviations, a standardized effect size of $d = 0.59$ was calculated. With a two-sided significance level of $\alpha = 0.05$ and a statistical power of 80%, the required total sample size was determined to be 94 participants (47 per group). Enrollment of 102 patients who developed postspinal hypotension ensured adequate power for the primary analysis.

All statistical analyses were performed using Jamovi (Version 2.6) and R (Version 4.4; R Core Team, Vienna, Austria). The distribution of continuous variables was assessed using graphical methods and formally tested for normality using the Shapiro–Wilk test. Data conforming to a normal distribution are summarized as mean $\pm$ standard deviation and were compared between groups using the independent-samples t test. Variables demonstrating non-normal distributions are presented as median with

interquartile range and were analyzed using the Mann–Whitney U test. Categorical data were examined using either the chi-square test or Fisher’s exact test, depending on expected cell frequencies.

To assess changes over time in maternal systolic blood pressure (SBP) and heart rate, a repeated-measures analysis of variance was applied. Violations of the sphericity assumption were addressed using the Greenhouse–Geisser adjustment. Effect size estimates were reported as partial eta squared (η^2p), and post hoc analyses were corrected for multiple comparisons using the Bonferroni approach. For nonparametric outcomes, effect sizes were expressed as rank-biserial correlation coefficients, while odds ratios with corresponding 95% confidence intervals were calculated where appropriate. All statistical tests were two-sided, with a significance threshold set at $P < 0.05$. For the primary outcome and key secondary neonatal outcomes, effect estimates (including Hodges-Lehmann median differences for continuous variables and odds ratios for categorical variables) with corresponding 95% confidence intervals were reported to provide measures of precision.

The primary efficacy analysis was restricted to randomized participants who developed postspinal hypotension requiring vasopressor treatment and subsequently received the allocated study medication. Participants were analyzed according to their original randomization assignment. This analytical population was selected to evaluate the comparative therapeutic effects of ephedrine and norepinephrine under clinically relevant treatment conditions.

There were no missing data for the primary or secondary outcomes; therefore, no imputation methods were applied. No prespecified or post hoc subgroup or sensitivity analyses were performed.

Anesthesia technique and perioperative management

All patients were instructed to fast for more than 8 hours before surgery. After hospital admission, two 20-gauge intravenous cannulas were inserted, and lactated Ringer’s solution was initiated at a rate of $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. This infusion was continued in the ward and preoperative holding area until transfer to the operating room.

In the preoperative assessment area, patients received intravenous prophylaxis consisting of pantoprazole 40 mg, ondansetron 4 mg, and cefazolin 2 g. After transfer to the operating room, all patients were monitored using standard modalities, comprising electrocardiography, noninvasive arterial blood pressure measurement, and pulse oximetry.

Spinal anesthesia was performed in the sitting position at the L2–3, L3–4, or L4–5 interspace using a 26-gauge or 27-gauge spinal needle. After confirmation of cerebrospinal fluid flow, 12 mg (2.4 mL) of 0.5% hyperbaric bupivacaine was administered intrathecally to all participants. Simultaneously, crystalloid coload was performed using $15 \text{ mL} \cdot \text{kg}^{-1}$ of crystalloid solution infused over 10 minutes with the aid of a pressure bag.

Following intrathecal injection, patients were positioned supine with approximately 15° left uterine displacement. Supplemental oxygen ($\text{FiO}_2 \approx 0.40$) was administered via a clear face mask. The level of sensory block was assessed using a pinprick test, and surgical incision was permitted once a bilateral sensory block at the T4–T5 dermatome level was achieved.

Hemodynamic Definitions and Management

Baseline maternal HR and SBP were defined as the average of two consecutive measurements obtained at 2-minute intervals before spinal anesthesia. Hypotension was defined as a decrease in SBP to less than 80% of baseline. Mean arterial pressure was recorded concurrently as a supportive hemodynamic parameter. Bradycardia was defined as a HR below 50 beats per minute and was treated with intravenous atropine at a dose of $10 \mu\text{g}\cdot\text{kg}^{-1}$.

In the ephedrine group, hypotension was treated with an intravenous bolus of ephedrine 5 mg, while in the norepinephrine group, a $5 \mu\text{g}$ bolus was administered. The selection of these specific rescue doses and the 1:1000 potency ratio was based on the dosing regimens previously established by Ngan Kee et al. and validated in the comparative methodology of Elnabity and Selim, aiming to provide comparable hemodynamic efficacy.^{13,17} Repeated boluses were administered at 1-minute intervals until the predefined blood pressure target was achieved.

Refractory hypotension was defined as the inability to maintain SBP at or above 80% of baseline or above 100 mmHg despite four consecutive bolus doses of the allocated vasopressor administered at 1-minute intervals. In such cases, open-label rescue therapy with intravenous epinephrine $10 \mu\text{g}$ was administered.

All interventions were delivered by attending anesthesiologists according to a standardized protocol, and no protocol deviations were observed. Apart from the allocated vasopressor, all participants received identical perioperative care, including spinal anesthesia technique, fluid management, monitoring, and adjunct medications.

Hemodynamic Monitoring, Data Collection, and Outcome Measures

Following intrathecal drug administration, maternal SBP and HR were recorded at 2-minute intervals and at 1-minute intervals during periods requiring vasopressor administration. The spinal-to-delivery interval and uterine incision-to-delivery interval were prospectively recorded for each patient. The number of hypotensive episodes, timing of interventions, total vasopressor dose administered, occurrence of bradycardia or tachycardia, atropine use, and episodes of refractory hypotension were prospectively recorded. Immediately following the delivery of the infant and umbilical cord clamping, a standardized protocol of oxytocin via slow intravenous infusion was administered to all participants to ensure consistency in postpartum management.

Umbilical cord blood samples were obtained immediately after delivery and before the neonate's first breath by double-clamping a segment of the umbilical cord. To ensure the accuracy of the sampling and avoid venous contamination, the umbilical artery was identified anatomically and visually confirmed by an experienced clinician. The UA samples (approximately 0.5–1 mL) were then aspirated and analyzed within 5 minutes within the operating suite using a calibrated Siemens RAPIDLab series automated blood gas analyzer (Siemens Healthineers, Erlangen, Germany). UA pH, partial pressure of carbon dioxide ($p\text{CO}_2$), bicarbonate (HCO_3^-), base excess, and lactate levels were recorded. Apgar scores at 1 and 5 minutes were assessed by a pediatrician blinded to group allocation.

The primary outcome was UA pH. Secondary outcomes included neonatal acid–base parameters, Apgar scores, neonatal HR measured after delivery, incidence and treatment of maternal hypotension, vasopressor requirements, maternal adverse events, and refractory hypotension requiring rescue epinephrine.

Results

A total of 180 parturients were assessed for eligibility, of whom 25 were excluded (20 did not meet the inclusion criteria and 5 declined to participate). The remaining 155 patients were randomized, with 77 allocated to the ephedrine group and 78 to the norepinephrine group. Following spinal anesthesia, postspinal hypotension was observed in 55 patients in each treatment arm. Patients who did not develop hypotension ($n = 22$ in the ephedrine group; $n = 23$ in the norepinephrine group) did not require vasopressor intervention and were therefore excluded from the subsequent efficacy analysis.

Following the intervention, 5 patients in the ephedrine group and 3 patients in the norepinephrine group were excluded due to clinical factors (meconium-stained amniotic fluid, cardiac anomalies, inadequate block height, or requirements for sedation). Ultimately, the final per-protocol analysis was conducted with 102 patients (ephedrine group, $n = 50$; norepinephrine group, $n = 52$), as detailed in the CONSORT flow diagram (Fig. 1).

Baseline maternal, obstetric, and neonatal characteristics were comparable between the ephedrine ($n = 50$) and norepinephrine ($n = 52$) groups (Table 1).

Table 1
Baseline Maternal and Neonatal Characteristics

Variable	Ephedrine 5 mg (n = 50)	Norepinephrine 5 µg (n = 52)
Maternal characteristics		
Age, years	30.1 ± 5.7	28.3 ± 5.1
Height, cm	160.2 ± 5.8	160.3 ± 6.0
Weight, kg	79.3 ± 12.4	81.3 ± 12.5
BMI, kg/m ²	30.8 ± 4.1	31.7 ± 4.6
Parity	3.0 (2.0–3.0)	3.0 (3.0–4.0)
Previous cesarean delivery	2.0 (2.0–3.0)	2.0 (2.0–4.0)
Preoperative fasting duration, min	685 (610–750)	653 (600–722)
Time of skin incision, min	5.0 (4.25–7.0)	5.0 (4.0–6.0)
Uterine incision to delivery, sec	45.5 (38.0–55.0)	47.0 (39.0–60.0)
Time to neonatal extraction, min	9.0 (7.0–10.75)	9.0 (8.0–11.0)
Duration of surgery, min	29.0 (25.25–31.0)	28.5 (25.0–30.25)
Neonatal baseline characteristics		
Gestational age, weeks	38.0 (38.0–38.6)	38.3 (38.0–38.6)
Birth weight, g	3238 ± 373	3243 ± 401
Sex		
Female	31 (62%)	30 (58%)
Male	19 (38%)	22 (42%)
Data are presented as mean ± SD, median (interquartile range), or frequency (%).		
No clinical or statistically significant differences were observed between the two groups for any baseline characteristics (P > 0.05)		
BMI = Body mass index.		
A statistically significant difference in UA pH was observed between the two treatment groups (Table 2). Median UA pH values were lower in the norepinephrine group than in the ephedrine group (7.33 [7.29–7.35] vs 7.35 [7.32–7.39]; P = 0.010, r = - 0.297). However, the occurrence of fetal acidosis defined as a UA pH < 7.20, was low in both groups and did not differ significantly between treatment arms (P = 0.614, OR = 2.12 [0.19–24.2])		

Table 2
Primary Neonatal Outcomes

Variable	Ephedrine 5 mg (n = 50)	Norepinephrine 5 µg (n = 52)	Effect Size / Test Statistic	P Value
Umbilical artery pH	7.35 (7.32– 7.39)	7.33 (7.29–7.35)	U = 914, r = –0.297	0.010
Neonatal acidosis	2 (4.0%)	1 (1.9%)	OR = 2.12 (0.19–24.2)	0.614
<p>Neonatal acidosis was defined as an umbilical arterial pH < 7.20.</p> <p>Data are presented as median (25th – 75th percentile) or frequency (%).</p> <p>Effect sizes are reported as rank-biserial correlation (r) or odds ratio (OR) with 95% confidence intervals.</p>				

UA pCO₂ (P = 0.006) and actual HCO₃⁻ (P = 0.033) differed significantly between groups, whereas base excess values were comparable (P = 0.828). UA lactate concentrations were similar in both groups (P = 0.733). Neonatal condition at birth, as assessed by Apgar scores at 1 minute (P = 0.783) and 5 minutes (P = 0.341), did not differ between groups. However, neonatal HR measured after delivery was significantly lower in the norepinephrine group (162.7 ± 16.1 beats/min) compared with the ephedrine group (169.9 ± 14.6 beats/min; P = 0.029). (Table 3).

Table 3
Neonatal Secondary Outcomes

Umbilical artery	Ephedrine 5 mg (n = 50)	Norepinephrine 5 µg (n = 52)	Med. Diff. (95% CI)	P Value
pCO ₂ ; mmHg	40.9 (37.5–44.7)	45.2 (40.4–52.4)	-4.2 [-6.9 to -1.4]	0.006
HCO ₃ ⁻ (act); mmol/L	22.7 (21.6–23.7)	23.4 (22.0–24.5)	-0.8 [-1.7 to -0.1]	0.033
Base excess (BE(B)); mmol/L	-2.5 (-3.9 to -1.7)	-2.7 (-3.5 to -1.7)	-0.1 [-0.7–0.6]	0.828
Lactate (mmol/L)	1.73 (1.43–2.09)	1.67 (1.46–2.19)	0.03 [-0.15–0.22]	0.733
Apgar score 1 min	8.0 (8.0–8.0)	8.0 (8.0–8.0)	0.0 [0.0–0.0]	0.783
Apgar score 5 min	9.0 (9.0–10)	9.5 (9.0–10.0)	0.0 [0.0–0.0]	0.341
Neonatal HR after delivery (bpm)	169.9 ± 14.6	162.7 ± 16.1	7.0 [0.0–13.0]	0.029
<p>pCO₂: Partial pressure of carbon dioxide</p> <p>HCO₃⁻: Bicarbonate</p> <p>Data are presented as median (quartiles) or mean ± standard deviation.</p> <p>Med. Diff: Hodges-Lehmann Median Difference.</p>				

Pre-delivery vasopressor dose was significantly higher in the ephedrine group (P = 0.002). Conversely, post-delivery vasopressor dose was lower in the ephedrine group (P = 0.025). The total vasopressor dose did not differ between treatment arms (P = 0.219). The frequency of hypotension episodes (P = 0.219) and the duration of hypotension (P = 0.134) were comparable between groups. Shock index values were similar (P = 0.657), consistent with comparable overall hemodynamic profiles. The drug-to-delivery interval was significantly shorter in the ephedrine group (P = 0.032). The incidence of refractory hypotension was low and did not differ between groups (P = 0.490). Atropine requirement occurred infrequently and were comparable between treatment groups (P = 0.618). (Table 4).

Table 4
Maternal Vasopressor and Hemodynamic Outcomes

Variable	Ephedrine 5 mg (n = 50)	Norepinephrine 5 µg (n = 52)	P Value
Pre-delivery vasopressor dose	10.0 (5.0–15.0)	5.0 (5.0–10.0)	0.002
Post-delivery vasopressor dose	0.0 (0.0–5.0)	5.0 (0.0–5.0)	0.025
Total vasopressor dose	15.0 (10.0–20.0)	10.0 (10–15)	0.219
Hypotension episodes, n	2.0 (2.0–4.0)	2.0 (2.0–3.0)	0.219
Duration of hypotension (min)	4.0 (2.75–5.0)	5.0 (3.0–8.0)	0.134
Shock index	0.78 (0.67–0.90)	0.79 (0.68–0.88)	0.657
Drug-to-delivery interval (min)	2.0 (2.0–4.0)	3.0 (2.0–4.25)	0.032
Refractory hypotension n (%)	1.0 (2%)	1.0 (2%)	0.490
Atropine requirement, n (%)	1.0 (2%)	3.0 (5.8%)	0.618
Data are presented as median (quartiles) or frequency (%).			
Shock index was calculated as heart rate divided by systolic blood pressure.			

The most frequently observed maternal adverse events were nausea, headache, and dizziness, with comparable incidences between the ephedrine and norepinephrine groups. Chest tightness and vomiting occurred less frequently and did not differ significantly between groups. Bradycardia and dyspnea were infrequent adverse events, with no statistically significant differences observed between treatment arms (Table 5).

Table 5
Maternal adverse events

Variable	Ephedrine 5 mg (n = 50)	Norepinephrine 5 µg (n = 52)	P Value
Nausea	22 (44%)	24 (46%)	0.845
Headache	12 (24%)	5 (9.6%)	0.051
Dizziness	9 (18%)	7 (13.5%)	0.593
Chest tightness	6 (12%)	8 (15.4%)	0.775
Vomiting	5 (10%)	3 (5.8%)	0.483
Bradycardia	2 (4.0%)	7 (13.5%)	0.092
Dyspnea	2 (4.0%)	8 (15.4%)	0.053
Maternal adverse events were recorded during the intraoperative period. Data are presented as frequency (%).			

Repeated-measures analysis identified a significant effect of time on both maternal SBP and HR following spinal anesthesia (SBP: Greenhouse–Geisser corrected, $F = 62.92$, $P < 0.001$, $\eta^2p = 0.398$; HR: $F = 9.14$, $P < 0.001$, $\eta^2p = 0.088$), reflecting marked temporal variation in maternal hemodynamic parameters.

For SBP, no significant time-by-group interaction was observed ($P = 0.087$), indicating similar temporal SBP patterns in the ephedrine and norepinephrine groups. However, a significant between-group main effect was noted, with higher overall SBP values in the ephedrine group ($F = 6.69$, $P = 0.011$, $\eta^2p = 0.066$). Conversely, analysis of HR demonstrated a significant time-by-group interaction ($F = 3.18$, $P = 0.023$, $\eta^2p = 0.051$), consistent with divergent temporal HR responses between treatment groups, whereas the main effect of group did not reach statistical significance ($P = 0.064$).

Post hoc analyses showed a significant reduction in SBP from baseline at early post-spinal time points in both groups (Bonferroni-adjusted $P < 0.001$), followed by gradual recovery over time, without clinically meaningful between-group differences at individual time points. For HR, post hoc comparisons demonstrated distinct within-group temporal changes, although no consistent between-group differences were observed after correction for multiple comparisons. These findings are illustrated in Fig. 2A and Fig. 2B.

Discussion

Our findings indicate that, compared with ephedrine, norepinephrine administration resulted in a modest but statistically significant reduction in median UA pH. Although the absolute difference was small, this

finding emerged despite comparable maternal blood pressure control and a similarly low incidence of categorical fetal acidosis. Crucially, this statistical difference did not reach a level of clinical relevance, as evidenced by comparable Apgar scores and the preserved low incidence of fetal acidosis.¹⁸ Therefore, the observed difference may reflect subtle physiological variation rather than a clinically meaningful neonatal effect. This observation places our results within the broader context of obstetric vasopressor research, where agents with predominant α -adrenergic activity have primarily been reported in comparisons with pure α -agonists, whereas direct comparisons with β -adrenergically active agents such as ephedrine remain limited.^{19,20} Previous studies by Ngan Kee et al. comparing norepinephrine with phenylephrine reported preserved fetal acid–base status; however, those comparisons did not include ephedrine, a vasopressor with stronger β -adrenergic activity.¹³ By incorporating ephedrine as a comparator, the present study enables differential β -adrenergic effects on fetal metabolism to be explored, thereby providing a physiologically plausible context for the observed divergence in fetal pH.²¹

Further insights arise from our analysis of secondary UA blood gas parameters. In our cohort, the norepinephrine group demonstrated significantly higher UA $p\text{CO}_2$ and actual HCO_3^- concentrations compared with the ephedrine group, while base excess and lactate levels remained comparable. This pattern may suggest that the observed difference in UA pH was potentially driven by alterations in $p\text{CO}_2$ handling rather than by metabolic acidemia.²² Similar cord-gas constellations have been described in prior physiologic studies, in which subtle impairments in placental gas exchange occurred despite preserved global fetal oxygenation and stable metabolic indices.²³ However, unlike those studies, which did not include a direct comparison with ephedrine, our findings suggest that these gas-exchange differences may persist even when maternal SBP is equivalently maintained with two different vasopressors, although the absence of differences in metabolic markers suggests limited clinical impact.

From a mechanistic perspective, the elevated $p\text{CO}_2$ observed with norepinephrine is consistent with reports suggesting that α -dominant vasopressors could theoretically influence uteroplacental vascular tone through redistribution of maternal cardiac output, potentially affecting placental CO_2 transfer despite adequate systemic blood pressure.²⁴ Recent evidence indicates that while vasopressors manage systemic hemodynamics, their specific impact on uteroplacental perfusion can vary based on local vascular resistance and autoregulatory mechanisms.²⁵ In contrast, it has been hypothesized that ephedrine's β -adrenergic activity may contribute to the preservation of uteroplacental perfusion.²⁶ The concurrent elevation in actual HCO_3^- in our study likely reflects partial metabolic compensation for this primary respiratory acid load. Importantly, the absence of differences in base excess and lactate is consistent with prior observations indicating that such physiologic differences do not necessarily translate into clinically relevant anaerobic metabolism or overt fetal hypoxia.²⁷ Accordingly, these mechanistic interpretations should be considered exploratory and interpreted in the context of the modest magnitude of the observed neonatal differences.

With respect to neonatal outcomes, neonatal HR measured after delivery was significantly lower in the norepinephrine group compared with the ephedrine group. This observation is consistent with known pharmacologic differences between the two agents. Ephedrine readily crosses the placenta and may stimulate fetal β -adrenergic receptors, which has been associated with transient increases in fetal heart rate.²⁸ In contrast, norepinephrine demonstrates limited placental transfer and a shorter effective half-life, leading to reduced direct fetal sympathomimetic stimulation.²⁹ When interpreted alongside our fetal acid–base findings, the lower neonatal HR observed with norepinephrine is consistent with reduced fetal β -adrenergic exposure; however, the clinical significance of this observation remains uncertain given the modest absolute differences and comparable neonatal outcomes between groups. Importantly, the absence of differences in Apgar scores indicates that these physiological distinctions did not translate into impaired immediate neonatal clinical condition.³⁰

Analysis of maternal hemodynamics demonstrated comparable effectiveness of ephedrine and norepinephrine in managing spinal anesthesia–induced hypotension, with similar frequencies and durations of hypotensive episodes. However, time-course analysis revealed that ephedrine was associated with higher overall mean SBP values, accompanied by a significantly greater pre-delivery vasopressor requirement. This pattern suggests that achieving target blood pressure with ephedrine may have required more frequent or higher bolus dosing, potentially reflecting differences in onset kinetics and dose–response characteristics compared with norepinephrine.³¹ Although higher mean SBP values could theoretically increase the likelihood of transient hypertension or reflex bradycardia, the similar incidence of maternal adverse events observed in our study indicates that these physiological differences were not associated with clear clinical consequences.

From a temporal perspective, the significant time $\times$ group interaction observed for maternal HR indicates that the temporal cardiovascular responses to ephedrine and norepinephrine differed over the course of observation. In our study, ephedrine's β -adrenergic stimulation was associated with sustained maternal heart rate, whereas norepinephrine maintained arterial pressure with comparatively less chronotropic effect, resulting in distinct HR trajectories. Similar differential HR patterns have been reported in prior comparative vasopressor studies and are consistent with the known pharmacodynamic profiles of these agents.³² Despite these physiological differences, the incidence of maternal adverse events including bradycardia and nausea was comparable between groups, suggesting that these temporal HR differences were not accompanied by clinically apparent maternal adverse effects under the conditions of the present study.

Our study has several methodological strengths, including its randomized, double-blinded design, which minimizes selection and observer bias and enhances internal validity. The direct head-to-head comparison of ephedrine and norepinephrine under standardized spinal anesthesia conditions, together with comprehensive assessment of umbilical arterial blood gas parameters and maternal hemodynamics, provides clinically relevant insight. Nevertheless, some limitations should be acknowledged. Maternal cardiac output and uteroplacental blood flow were not directly measured, and

the study population was limited to low-risk parturients undergoing elective cesarean delivery, which may limit generalizability to emergency settings or higher-risk populations. In addition, although statistically significant differences were observed in some neonatal acid–base variables, the modest absolute magnitude of these differences and the absence of clear differences in clinically relevant neonatal outcomes should be considered when interpreting the findings.

An additional limitation relates to the analytical population. Although randomization was performed before spinal anesthesia, the final analysis was restricted to patients who subsequently developed postspinal hypotension requiring vasopressor treatment. Because the analyzed cohort was defined by a post-randomization event, some degree of selection bias and reduced preservation of randomization benefits cannot be excluded.

Conclusion

Norepinephrine was associated with a statistically significant reduction in umbilical arterial pH compared with ephedrine; however, the absolute magnitude of this difference was modest and remained within normal physiological limits. This statistical finding did not translate into clinically meaningful differences in the incidence of neonatal acidosis, Apgar scores, or overall fetal metabolic status. Maternal hemodynamic control and safety profiles were comparable between the two vasopressors. These findings suggest that under standardized clinical conditions, norepinephrine represents a clinically acceptable and effective alternative to ephedrine for the management of postspinal hypotension during elective cesarean delivery, offering a similar neonatal safety profile.

Declarations

Authors' contributions

Acquisition of data: R.U., A.K., S.T., F.A., A.K.O., M.Y., Y.B

Data analysis: M.Ö., O.U., S.K.

Drafting of manuscript: M.Ö.

Revision of manuscript: M.Ö., O.U

Final approval: M.Ö., R.U., A.K., S.T., F.A., A.K.O., M.Y., Y.B., O.U., S.K.

All authors were involved in the concept, study design, and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

The study protocol was approved by the Harran University Clinical Research Ethics Committee (April 28, 2025; approval no. HRÜ/25.08.38). Written informed consent was obtained from all participants prior to

enrollment.

Consent for publication

Not applicable.

Declarations of interest

The authors declare that they have no competing interests.

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Data Availability

The study protocol, prespecified statistical analysis plan, anonymized raw data, data dictionary, and statistical code supporting the findings of this study are available from the corresponding author upon reasonable request.

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Figures

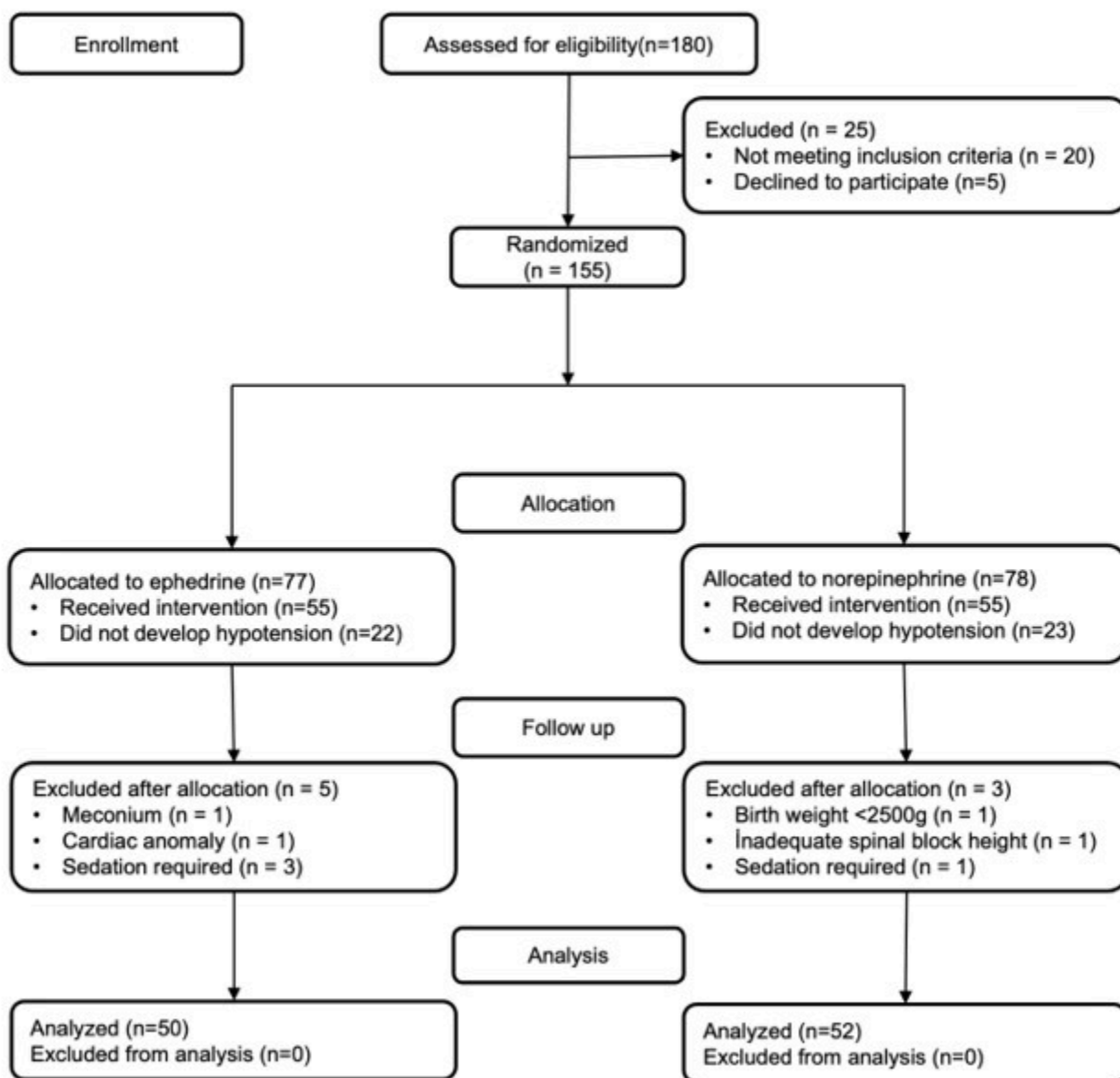


Figure 1

Consolidating Standards of Reporting Trials (CONSORT) flow diagram of study recruitment and analysis.

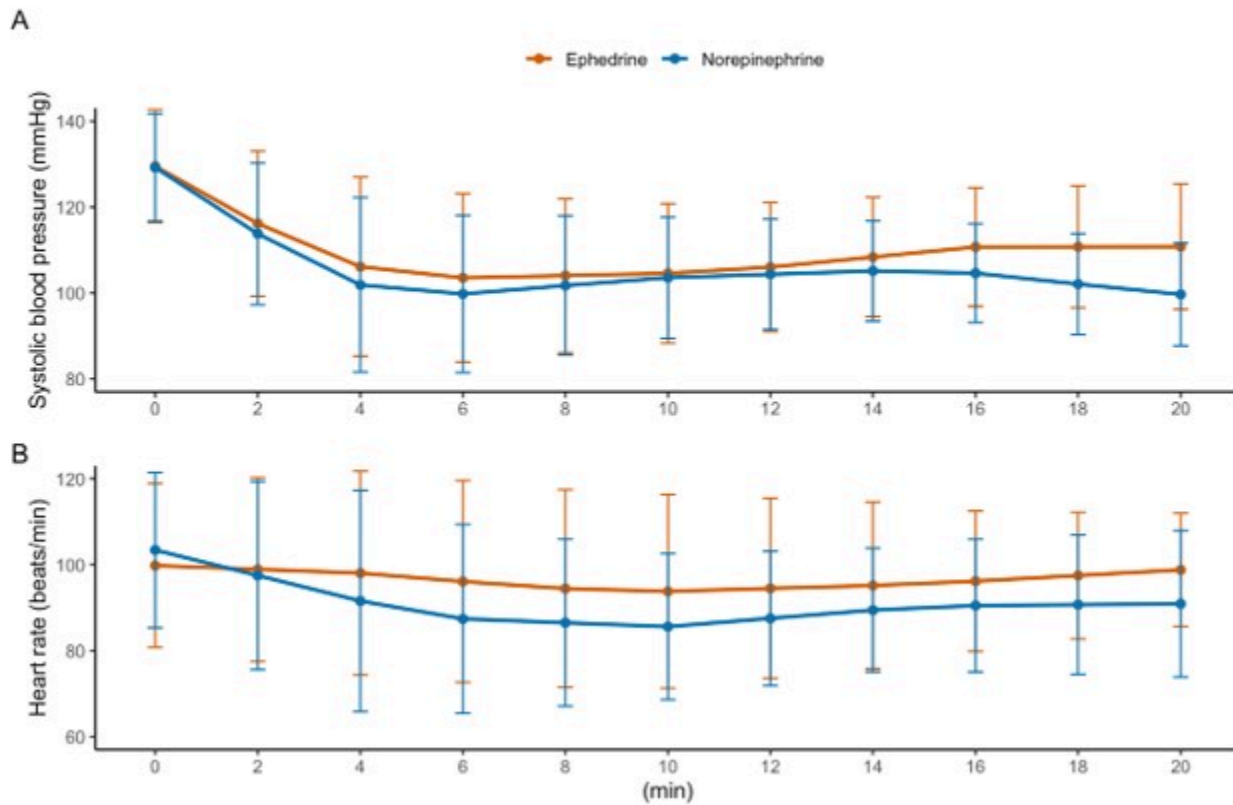


Figure 2

Time-course changes in maternal hemodynamics following spinal anesthesia.

(A) Maternal systolic blood pressure and (B) maternal heart rate measured at baseline and at 2-minute intervals up to 20 minutes after spinal anesthesia in the ephedrine and norepinephrine groups. Data are presented as mean $\pm$ standard deviation.