Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Determination of ED90s of Phenylephrine and Norepinephrine Infusion for Strict Blood Pressure Management Targets in Preeclamptic Patients Undergoing Cesarean Section: A Randomized Sequential Allocation Study

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Background: The consensus recommends maintaining the patient's systolic blood pressure at or above 90% of the baseline value, and highlights the use of vasopressors as the primary strategy for preventing and managing hypotension during cesarean section. This study was aimed to determine the ED90 of prophylactic infusions of norepinephrine and phenylephrine in preeclamptic patients under strict blood pressure management target (maintaining ≥90% of the baseline value).

Methods: 60 preeclamptic patients were randomly assigned to either the norepinephrine or the phenylephrine group. The initial patients received an infusion of norepinephrine at 0.05 μg/kg/min or phenylephrine at 0.5 μg/kg/min. For subsequent patients, infusion rates were adjusted in increments or decrements of 0.01 or 0.1 μg/kg/min, respectively, to achieve strict blood pressure management targets before delivery. Secondary outcomes included patients' adverse events, umbilical artery blood gas analysis, and newborns' Apgar scores.

Results: The isotonic regression analysis revealed that the ED90 values of norepinephrine and phenylephrine infusions required to maintain a strict blood pressure management targets were 0.076 μg/kg/min (95% CI, 0.070–0.080) and 0.900 μg/kg/min (95% CI, 0.850–0.950), respectively. The secondary outcomes between groups were comparable.

Conclusion: Under strict blood pressure management target in preeclamptic patients undergoing cesarean section, the ED90 values for norepinephrine and phenylephrine infusions are 0.076 μg/kg/min and 0.900 μg/kg/min, respectively.

Trial Registration: This study was registered at ClinicalTrials.gov on November 28, 2023 (No. NCT06158022).

Keywords: Preeclampsia, cesarean section, strict blood pressure management target, norepinephrine, phenylephrine

Introduction

It is estimated that by 2030, the global average rate of cesarean sections will rise from the current 21.1% to approximately 30%, with the number surpassing 38 million annually.[1] According to the practice guidelines issued by the American College of Obstetricians and Gynecologists (ACOG), spinal anesthesia is recommended as the preferred anesthetic technique for cesarean sections in the absence of contraindications, compared with general anesthesia.[2,3] Hypotension represents the most prevalent anesthetic complication during cesarean section among normotensive patients, with the proportion reaching up to 62.1%.[4] In contrast, the proportion is lower at 37.8% among preeclamptic patients in the absence of preventive interventions.[5] Severe and prolonged hypotension may result in adverse outcomes, including diminished placental blood flow, and fetal intrauterine hypoxia, thereby compromising the safety of both the patients and the fetus.[6,7] Although the

Received: 9 June 2025
Accepted: 26 October 2025
Published: 1 November 2025

incidence of hypotension is lower in preeclamptic patients, its occurrence can further exacerbate the already compromised uteroplacental perfusion.[8]

The consensus regarding blood pressure management during cesarean section recommends maintaining the patient's systolic blood pressure (SBP) at or above 90% of the baseline value following spinal anesthesia, while ensuring it does not fall below 80% of the baseline value. Additionally, it highlights the use of vasopressors as the primary strategy for preventing and managing hypotension induced by spinal anesthesia.[9] Vasopressors, particularly α-receptor agonists, are effective in directly counteracting arterial dilation and decreased peripheral vascular tone.[10,11] This approach aids in stabilizing the patient's blood pressure and cardiac output while also preventing insufficient placental perfusion due to hypotension.[12] Norepinephrine is regarded as an alternative to phenylephrine in obstetric anesthesia, given its effective α-receptor agonist properties and mild β-receptor agonist effects, which help prevent bradycardia and sustain cardiac output.[13]

Currently, the evidence supporting preventive and rescue strict blood pressure management targets to maintain a patient's SBP at or above 90% of the baseline value remains limited. Consequently, we conducted a randomized sequence allocation dose-finding study to determine the ED90 of prophylactic infusions of norepinephrine and phenylephrine in preeclamptic patients undergoing cesarean section under strict blood pressure management targets.

Methods

This double-blind study received approval from the Ethics Committee of the General Hospital of Ningxia Medical University (No. KYLL-2023-0399-3) and was conducted between October 2024 and May 2025. It was prospectively registered on ClinicalTrials.gov (No. NCT06158022) prior to the initiation of the trial and strictly followed the principles outlined in the Declaration of Helsinki and the CONSORT guidelines. All patients provided written informed consent before undergoing any intervention. The study included patients aged 18–45 years, primipara or multipara, classified as ASA II–III, with a gestational age of ≥ 32 weeks, who were diagnosed with preeclampsia according to the ACOG guidelines,[14] scheduled for cesarean section under spinal anesthesia. Patients with a baseline SBP ≥ 160 mmHg, body height < 150 cm, body weight > 100 kg or body mass index (BMI) ≥ 40 kg/m², eclampsia, chronic hypertension, fetal distress, or known fetal abnormalities were excluded.

The patient was transferred to the operating room and underwent non-invasive hemodynamic monitoring, which included an electrocardiogram (ECG), non-invasive blood pressure, and transcutaneous pulse oxygen saturation (SpO2). Baseline values were established by averaging three consecutive measurements taken at 2-minute intervals while the patient was in a resting state. Continuous hemodynamic monitoring was performed at 1-minute intervals prior to fetal delivery and at 5-minute intervals post-delivery. Crystalloids and vasopressors were administered via an 18G indwelling venous catheter. Patients did not receive a preload but were administered a 3 mL/kg crystalloid coload infusion immediately upon induction of spinal anesthesia. Post-delivery fluid management was overseen by the responsible anesthesiologist.

Based on the grouping protocol, patients were randomly assigned to either the norepinephrine group or the phenylephrine group. The random number series were generated using SPSS, with each group comprising 30 sequences and a 1:1 allocation ratio applied. One researcher, who was not involved in the administration of spinal anesthesia and was tasked with preparing vasopressors for the patients, conducted the blinding process, which included group allocation (via opaque envelopes), and setting of infusion rates. Patients and the responsible anesthesiologist remained blinded to the specific drug intervention.

The spinal anesthesia was administered by an experienced obstetric anesthesiologist. The patient was positioned laterally, and after assessment, the needle was inserted at the L3-4 interspace. Upon confirmation of the subarachnoid space, 12.5 mg of 0.5% bupivacaine was injected. Subsequently, the patient was placed in the supine position with a 15° left lateral tilt of the surgical bed. The operation commenced only after repeated evaluations confirmed that the lowest level of the block was at T6. At the onset of spinal anesthesia, vasopressor was administered immediately. The first patients in both groups received infusions of norepinephrine at 0.05 μg/kg/min and phenylephrine at 0.5 μg/kg/min, respectively. For subsequent patients, the dosages were adjusted according to whether the strict blood pressure management targets (maintaining ≥90% of the baseline value) could be achieved prior to delivery. If the target was successfully maintained, the infusion rates of norepinephrine and phenylephrine for the subsequent patient were decreased by 0.01 μg/kg/min and 0.1 μg/kg/min, respectively. Conversely, if the target was not maintained, the infusion rates were increased by 0.01 μg/kg/min and 0.1 μg/kg/min, respectively.

The primary outcome measure was the ED90 values of norepinephrine and phenylephrine infusions required to maintain a strict blood pressure management target. Secondary outcomes included the incidence of hypotension and severe hypotension, defined as SBP falling below 90% or 60% of the baseline value, respectively. In cases where SBP fell below 80%, rescue treatment was administered according to group assignment: either 6 μg of norepinephrine or 60 μg of phenylephrine. Document the incidence of bradycardia (heart rate < 60 beats/min), and administered 0.5 mg of atropine if the heart rate fell below 50 beats/min. Document the incidence of hypertension (SBP > 120% of the baseline value), and discontinued the infusion of norepinephrine or phenylephrine if hypertension occurred or SBP exceeded 160 mmHg until it normalizes. Urapidil was intended for use in managing blood pressure if maternal SBP could not be lowered to baseline levels or within a safe range within a short time after discontinuation of norepinephrine or phenylephrine infusion. Additional outcomes include the incidence of nausea and vomiting, as well as umbilical artery pH, PCO_2, PO_2, base excess, and Apgar scores at 1 and 5 minutes post-delivery.

Statistical Analysis

A comprehensive review of statistical methodologies and a clinical randomized sequential allocation study indicates that a sample size of 20 to 40 patients, with at least seven crossover transition points, can yield a reliable estimation of the target dose.[15,16] Thus, 30 patients who were expected to have at least ten crossover transition points were included in our study.

The Shapiro–Wilk test was employed to evaluate whether continuous variables followed a normal distribution. For normally distributed continuous variables (age, height, weight, body mass index, maternal baseline systolic blood pressure and heart rate, anesthesia or incision to fetal delivery interval, umbilical artery pH, PCO_2, PO_2, and base excess), intergroup comparisons were performed using the Student's *t*-test (homogeneity of variance was assessed using Levene's test; if this assumption was violated, Welch's *t*-test or a nonparametric alternative was employed) with results presented as mean ± standard deviation. For non-normally distributed continuous variables (gestational age, sensory block, Apgar score at 1 min and 5min), the Mann–Whitney *U*-test was utilized for intergroup comparisons, and results were expressed as median [interquartile range, IQR]. Categorical variables were compared between groups using the chi-square test, with findings reported as percentages. The ED90 of norepinephrine and phenylephrine infusions for maintaining strict blood pressure management targets was analyzed using the isotonic regression model. All aforementioned analyses were conducted using IBM SPSS Statistics version 25.0. A P value < 0.05 was considered indicative of statistical significance.

Results

Seven patients were excluded based on the inclusion criteria, resulting in a total of 60 patients being enrolled, with 30 patients in each group. The CONSORT flowchart (Figure 1) illustrates the patient recruitment process. No statistically significant differences were observed between groups regarding demographic characteristics, baseline values, application of preoperative antihypertensive medication, anesthesia-related characteristics, intraoperative urine volume, or intraoperative crystalloid infusion volume (Table 1).

The infusion sequences of norepinephrine and phenylephrine administered to maintain strict blood pressure management targets in the two groups of patients prior to delivery are illustrated in Figure 2. The results of the isotonic regression analysis revealed that the ED90 of norepinephrine and phenylephrine infusions in the two groups were 0.076 μg/kg/min (95% CI, 0.070–0.080) and 0.900 μg/kg/min (95% CI, 0.850–0.950), respectively.

There were no statistically significant differences between groups with respect to patient adverse events, umbilical artery blood gas analysis, and neonatal Apgar scores (Table 2).

Discussion

The aim of this study was to determine the ED90 of prophylactic infusions of norepinephrine and phenylephrine in preeclamptic patients under strict blood pressure management targets; the ED90 values, reported for the first time, were 0.076 μg/kg/min (95% CI, 0.070–0.080) and 0.900 μg/kg/min (95% CI, 0.850–0.950), respectively.

Due to the restrictive fluid management strategies in preeclamptic patients, vasopressors have emerged as the preferred approach for the prevention and management of hypotension during cesarean section. The efficacy and safety of norepinephrine and phenylephrine infusions in maintaining blood pressure in preeclamptic patients have been verified in previous

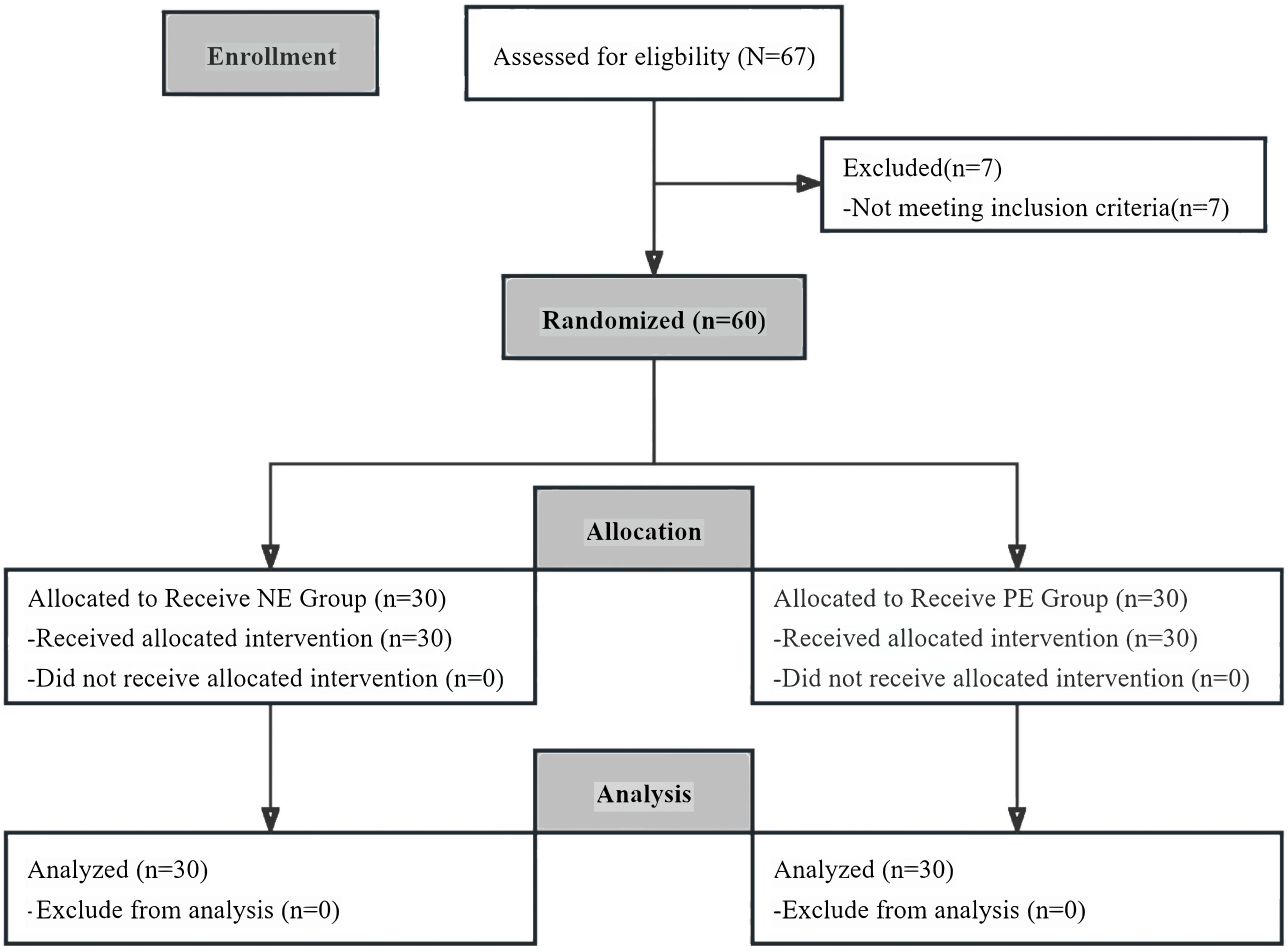

Figure 1 The CONSORT flow diagram.

studies.[17] To date, there is a lack of evidence regarding the ED90 values of norepinephrine and phenylephrine infusions required to maintain a strict blood pressure management target. Tan et al[18] investigated the ED90 values of phenylephrine or norepinephrine infusions for maintaining SBP in preeclamptic patients at greater than 80% of the baseline value. These values

Table 1 Demographic and Anesthesia Characteristics

	Phenylephrine Group (n=30)	Norepinephrine Group (n=30)	*P* value
Age, years	30.60±4.92	32.60±3.93	0.087
Height, cm	162.13±4.93	160.90±6.49	0.410
Weight, kg	79.80±11.04	78.24±16.18	0.665
Body mass index, kg/m^2	30.36±4.02	30.09±5.27	0.822
Gestational age, weeks	37[35, 39]	37[36, 38]	0.934
Preeclampsia with severe features, n (%)	11 (36.7)	12 (40.0)	0.791
Maternal baseline SBP, mmHg	141.80±11.45	141.47±8.88	0.900
Maternal baseline HR, bpm	91.63±14.91	91.87±11.87	0.947
Sensory block	T6[T4, T6]	T5[T4, T6]	0.373
Application of preoperative antihypertensive medication	24 (80.0)	26 (86.7)	0.731
Anesthesia to fetal delivery interval, min	16.00±3.49	15.23±2.98	0.364
Incision to fetal delivery interval, min	3.27±1.51	3.40±1.67	0.747
Intraoperative urine volume, mL	150[100, 200]	200[100, 200]	0.239
Intraoperative crystalloid infusion volume, mL	750 [500, 800]	700 [600, 800]	0.517

Note: Values are mean ± SD, median [IQR] or n (%).

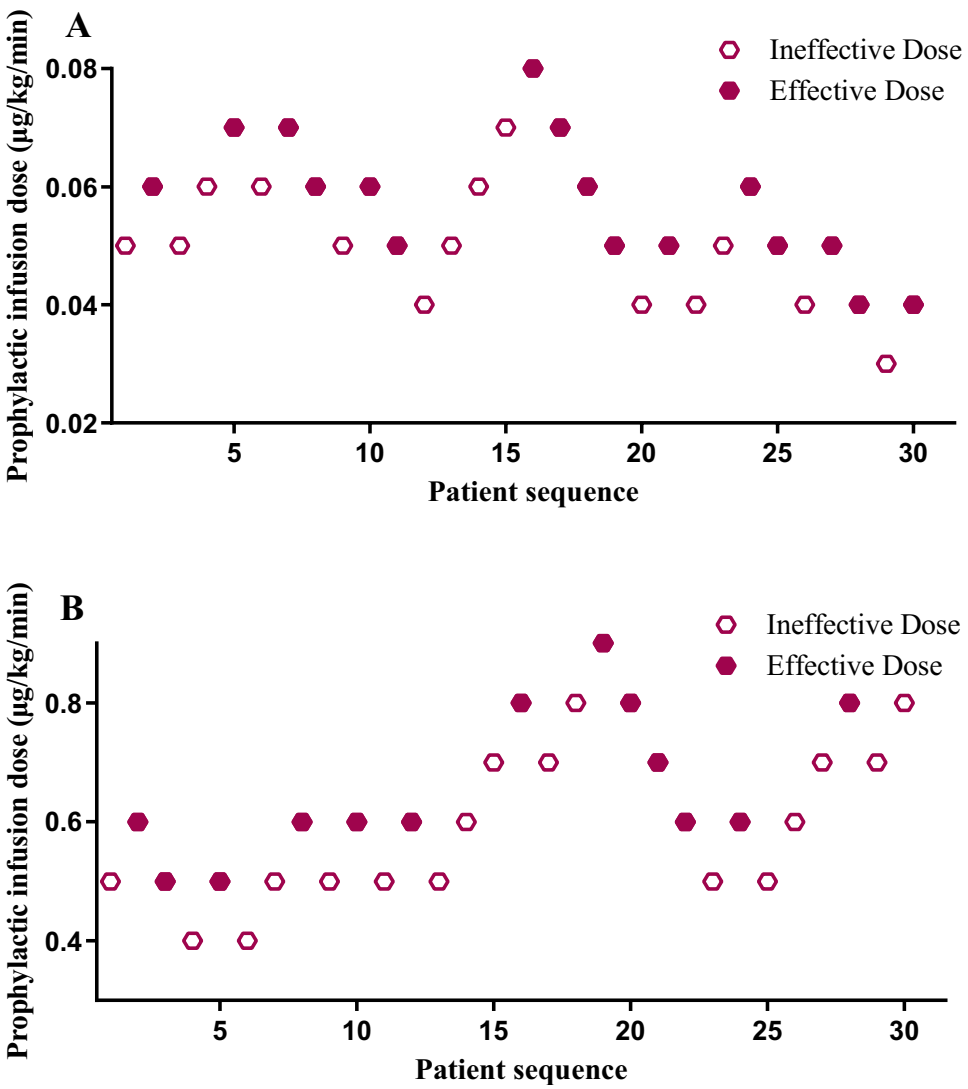

Figure 2 The infusion sequences of norepinephrine (**A**) and phenylephrine (**B**) administered to maintain strict blood pressure management targets in the two groups of patients prior to delivery.

were determined to be 0.597 μg/kg/min (95% CI: 0.582–0.628) and 0.054 μg/kg/min (95% CI: 0.053–0.056), respectively. A randomized, dose-response study conducted by Chen et al[5] demonstrated that the ED90 value for norepinephrine infusion was 0.065 μg/kg/min (95% CI: 0.048–0.108). In our investigation, the ED90 values for both norepinephrine and phenylephrine were significantly higher than those reported in previous studies, which may be attributed to the strict target set for maintaining maternal blood pressure. A similar trend was seen in normotensive patients.[19,20]

Given that spinal anesthesia can decrease uteroplacental resistance and cardiac afterload while enhancing blood flow to the villi, it has been recognized as a preferred anesthetic approach in preeclamptic patients.[9,14] In certain cases, spinal anesthesia may result in relatively severe and prolonged hypotension, thereby impairing compromised perfusion and adversely affecting neonatal outcomes.[21,22] However, in preeclamptic patients, insufficient extravillous trophoblast invasion and inadequate spiral artery remodeling result in increased resistance in uterine spiral arteries, leading to significantly elevated blood pressure and peripheral vascular resistance. This condition is associated with a lower incidence and severity of maternal hypotension and reduced need for vasopressors.[23] In addition, under a stricter blood pressure management target, a higher dosage of vasopressor may be necessary. Therefore, in preeclamptic patients, the administration of low-dose prophylactic vasopressors combined with variable infusion rates and small-dose rescue boluses is more advantageous for maintaining maternal hemodynamic stability.

https://doi.org/10.2147/DDDT.S545813

Table 2 Maternal Adverse Events and Neonatal Outcomes

	Phenylephrine Group (n=30)	Norepinephrine Group (n=30)	*P* value
Maternal outcomes			
Post-spinal anesthesia hypotension, n (%)	15(50.0)	14(46.7)	0.796
Severe post-spinal anesthesia hypotension, n (%)	0(0.0)	1(3.3)	0.500
Bradycardia, n (%)	3(10.0)	2(6.7)	1.000
Hypertension, n (%)	4(13.3)	2(6.7)	0.671
Nausea or vomiting, n (%)	3(10.0)	4(13.3)	1.000
Neonatal outcomes			
Umbilical artery pH	7.31±0.02	7.31±0.02	0.870
Umbilical artery pH < 7.2, n (%)	0(0.0)	0(0.0)	1.000
Umbilical artery PCO_2, mmHg	45.27±5.47	44.71±6.62	0.729
Umbilical artery PO_2, mmHg	21.76±6.53	23.32±6.70	0.369
Umbilical artery base excess, mmol/L	−3.25±2.23	−3.62±1.63	0.478
Apgar score at 1 min	9 [8, 9]	9 [8, 9]	0.061
Apgar score at 1 min < 7, n (%)	0(0.0)	0(0.0)	1.000
Apgar score at 5 min	10 [9, 10]	10 [9, 10]	0.065
Apgar score at 5 min < 7, n (%)	0(0.0)	0(0.0)	1.000

Note: Data are presented as n (%), mean ± SD or median [IQR].

This study possesses certain limitations. First, as a single-center and small-sample investigation, the findings may lack generalizability to broader populations. Second, the intermittent blood pressure monitoring method employed in this study may lack sufficient sensitivity to effectively guide vasopressor administration, thereby complicating the establishment of optimal intervention strategies. This often results in either overtreatment or undertreatment of patients. Third, for patients with preoperative high maternal SBP (>160 mmHg), cardiovascular or other systemic comorbidities, and those exhibiting hemodynamic instability despite antihypertensive therapy, the use of prophylactic vasopressors requires individualized assessment and management to ensure maternal and fetal safety.

In conclusion, when adhering to strict blood pressure management targets in preeclamptic patients undergoing cesarean section, the ED90 values for norepinephrine and phenylephrine infusions are 0.076 μg/kg/min and 0.900 μg/kg/min.

Data Sharing Statement

The data that support the study findings are available from the corresponding author upon reasonable request.

Ethics Approval

This double-blind study received approval from the Ethics Committee of the General Hospital of Ningxia Medical University (No. KYLL-2023-0399-3).

Funding

This trial was funded by the Ningxia Natural Science Foundation (No. 2024AAC03643), Yinchuan, China.

Disclosure

The authors report no conflicts of interest in this work.

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