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CLINICAL TRIAL REPORT

Determination of ED90s of Phenylephrine and Norepinephrine Infusion for Prevention of Spinal Anesthesia-Induced Hypotension in Patients with Preeclampsia During Cesarean Delivery

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Background: Vasopressors remain an important strategy for managing spinal anesthesia-induced hypotension in women with preeclampsia. The aim of this study was to investigate the ED90s and efficacy ratio of phenylephrine and norepinephrine in managing spinal anesthesia-induced hypotension in women with preeclampsia during cesarean delivery.

Methods: 60 women with preeclampsia, who underwent cesarean delivery, were randomly assigned to receive either a continuous intravenous infusion of phenylephrine or norepinephrine following spinal anesthesia. The initial dosage of phenylephrine or norepinephrine for the first women was 0.5 or 0.05 μg/kg/min, respectively, and subsequent infusion dosages were adjusted based on their efficacy in preventing spinal anesthesia-induced hypotension (defined as a systolic blood pressure less than 80% of the baseline level). The incremental or decremental doses of phenylephrine or norepinephrine were set at 0.1 or 0.01 μg/kg/min. The primary outcomes were the ED90s and efficacy ratio of phenylephrine and norepinephrine infusions for preventing spinal anesthesia-induced hypotension prior to delivery.

Results: The results obtained from isotonic regression analysis revealed that the ED90 values of the phenylephrine and norepinephrine group for preventing spinal anesthesia-induced hypotension were 0.597 (95% CI: 0.582–0.628) and 0.054 (95% CI: 0.053–0.056) μg/kg/min, respectively, with an efficacy ratio of 11.1:1. The results of Probit regression analysis revealed that the ED90 values were determined to be 0.665 (95% CI: 0.576–1.226) and 0.055 (95% CI: 0.047–0.109) μg/kg/min, respectively, with an efficacy ratio of 12.1:1.

Conclusion: The administration of 0.6 μg/kg/min phenylephrine and 0.05 μg/kg/min norepinephrine has been found to effectively manage a 90% incidence of spinal anesthesia-induced hypotension in women with preeclampsia.

Keywords: ED90, phenylephrine, norepinephrine, spinal anesthesia-induced hypotension, preeclampsia, cesarean delivery

Introduction

The administration of spinal anesthesia is a crucial method for performing cesarean delivery in pregnant women. However, its implementation can lead to significant hemodynamic changes, such as decreased peripheral vascular resistance and notable alterations in blood pressure and cardiac output. If not promptly addressed, these changes may lead to adverse events in both the mother and newborns, ultimately impacting the overall outcome.[1–3] The low resistance of the uterine placenta in normotensive women facilitates the entry of maternal blood into the placental circulation through the villi, thereby promoting fetal growth and meeting its nutritional requirements.[4] The lack or failure of villi invasion in women with preeclampsia, however, leads to a significant increase in placental resistance. This subsequently results in elevated systemic vascular resistance and blood pressure, as well as placental hypoperfusion. Consequently,

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adverse events such as neonatal growth retardation may occur[5,6] The paradoxical state arises where maternal blood pressure is elevated while placental perfusion often remains inadequate. Consequently, spinal anesthesia-induced hypotension can significantly impact the maternal hemodynamic stability and further exacerbate placental malperfusion, potentially influencing the outcome of both mother and newborns.

Although vasopressors remain an important strategy for managing spinal anesthesia-induced hypotension in women with preeclampsia, there are concerns regarding their prophylactic application due to potential adverse effects such as dose-dependent bradycardia impacting maternal cardiac output and uteroplacental perfusion, as well as a possible increase in blood pressure leading to hemorrhagic stroke.[6,7] Currently, there is limited evidence on the use of vasopressors such as phenylephrine and norepinephrine for preventing spinal anesthesia-induced hypotension in women with preeclampsia. However, prophylactic infusions of these vasopressors for spinal anesthesia-induced hypotension at appropriate doses have been shown to be safe and effective.[8] The prophylactic use of norepinephrine provides greater hemodynamic stability due to its additional activation of β receptors.[9] The aim of this study was to investigate the ED90s and efficacy ratio of phenylephrine and norepinephrine in managing spinal anesthesia-induced hypotension in women with preeclampsia during cesarean delivery.

Methods

The Ethics Committee of the Fifth People's Hospital of Huaian, Jiangsu, China, granted approval for this study in June 2023 (No. HAWY-KY-2023-017-01). This clinical trial, conducted from June 2023 to February 2024, was in accordance with the Declaration of Helsinki. Prior to inclusion, all pregnant women provided informed consent and were registered in the Chinese Clinical Trials (No. ChiCTR2300072579). The inclusion criteria included singleton pregnant women with preeclampsia (the diagnostic criteria were based on the 2013 and 2020 American College of Obstetricians and Gynecologists Guidelines)[10,11] classified as ASA Class II or III who underwent cesarean delivery under spinal anesthesia. The exclusion criteria included contraindication to spinal anesthesia as well as chronic hypertension or other cardiovascular/cerebrovascular diseases, eclampsia, and severe fetal distress.

The pregnant women underwent a minimum 4-hour fasting period, refrained from drinking for 2 hours, and did not receive preoperative medication or fluids. Upon entering the operating room, non-invasive monitoring of blood pressure, heart rate, and pulse oxygen saturation was initiated while an 18G needle was inserted into the peripheral vein. Maternal blood pressure and heart rate were monitored in a resting state with three measurements taken (at intervals of 2 minutes) to determine the average values as baseline blood pressure and heart rate. Spinal anesthesia was administered in the lateral position via the L2-3 intervertebral space. After confirming the presence of cerebrospinal fluid, all pregnant women received a 12.5 mg 0.5% w/v bupivacaine followed by placement of a catheter measuring 3–4 cm in length in the epidural space. Subsequently, they were positioned supine at an angle of 15° to the left of the uterus to alleviate pressure on the inferior vena cava and abdominal aorta. The sensory block level was assessed using a sterile syringe needle and ensured not to be below T6. Following anesthesia induction, crystalloid was administered at a rate of 5–6 mL/kg/h. Non-invasive blood pressure and heart rate were recorded at 1-minute intervals immediately after spinal anesthesia until the delivery of baby, and then transitioned to monitoring every 5 minutes.

Maternal randomization was conducted prior to the implementation of the clinical study, using a random series generated according to SPSS. The pregnant women were paired in a one-to-one manner and placed sequentially in opaque boxes, resulting in two groups: the phenylephrine group and the norepinephrine group. Following spinal anesthesia, either phenylephrine or norepinephrine was immediately administered by continuously intravenously infusing based on the assigned group. Both the pregnant women and the anesthesiologist responsible for anesthesia management were blinded to the group allocation. The concentrations of phenylephrine and norepinephrine were diluted to 75μg /mL and 6μg /mL, respectively, using normal saline. Subsequently, they were stored in a transparent and unmarked syringe with a capacity of 50mL. Another researcher (not involved in anesthesia management), who was not blinded to the assigned group and the current dose being administered, pre-placed the syringe on the infusion pump and set the pump speed (the display interface was covered with an opaque black paper). The initial dose of phenylephrine for the first woman in the phenylephrine group was 0.5 μg/kg/min, and subsequent infusion doses were adjusted based on whether this dosage could effectively prevent spinal anesthesia-induced hypotension (defined as a systolic blood pressure less

than 80% of the baseline level) before fetal delivery. For each subsequent case, if the maternal blood pressure could be maintained at a level 80% higher of the baseline level, the infusion rate of phenylephrine was decreased by 0.1 μg/kg/min; conversely, if it could not be maintained, the infusion rate was increased by 0.1 μg/kg/min. The norepinephrine group was subjected to the same rules. The initial dose of norepinephrine for the first woman in the norepinephrine group was 0.05 μg/kg/min. For each subsequent case, if the maternal blood pressure could be maintained at a level 80% higher of the baseline level, the infusion rate of norepinephrine was decreased by 0.01 μg/kg/min; conversely, if it could not be maintained, the infusion rate was increased by 0.01 μg/kg/min. Upon delivery in the operating room, all newborns are promptly transferred to neonatologists for further evaluation and treatment.

The primary outcomes were the ED90s of phenylephrine and norepinephrine infusions for preventing spinal anesthesia-induced hypotension prior to delivery. Other outcomes included the incidence of spinal anesthesia-induced hypotension and severe hypotension, defined as systolic blood pressure less than 80% and 60% of baseline levels, respectively. In case these adverse events occurred, correction was administered with a dosage of 50 μg phenylephrine and 5 μg norepinephrine, according to the assigned group. Hypertension was defined as a systolic blood pressure > 120% of the baseline level. When hypertension occured or the systolic blood pressure exceeded 160mmHg, the administration of phenylephrine or norepinephrine was temporarily discontinued until the systolic blood pressure fell below 120% of the baseline or < 160mmHg. In addition, we have prepared phentolamine or urapidil to prevent further or persistent increased in maternal blood pressure. Atropine 0.5mg was administered when the maternal heart rate was less than 50 beats per minute. The incidence of nausea and vomiting was also recorded. Additionally, neonatal umbilical artery blood gas parameters including pH, base excess, and Apgar scores were recorded.

Statistical Analysis

Based on previously reported literature, a sample size of 20–40 cases and a minimum of six pairs of sequence reversals is considered sufficient for the analysis of up-and-down sequence allocation.[12,13] Therefore, we included 30 women in each group (phenylephrine and norepinephrine) for the final analysis.

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Independent sample *t*-tests were conducted to compare groups that followed a normal distribution, with results reported as mean ± standard deviation (SD). Mann–Whitney *U*-tests were conducted to compare groups that did not adhere to a normal distribution, and the results were expressed as median and interquartile range (IQR). Categorical variables underwent chi-square tests for comparison and were presented as percentages (%). The isotonic regression analysis (performed in R language) and Probit regression analysis (performed in SPSS) were conducted to calculate the ED90s of phenylephrine or norepinephrine infusion for preventing spinal anesthesia-induced hypotension prior to delivery. Other data were analyzed using IBM SPSS Statistics version 23.0 (IBM SPSS, Inc, Chicago, IL). A significance level of $P < 0.05$ indicated a statistically significant difference.

Results

Nine pregnant women were excluded based on the inclusion criteria, resulting in a final analysis of 60 women with 30 in each group (phenylephrine and norepinephrine group). The inclusion process is illustrated in Figure 1.

The maternal characteristics, including age, BMI, baseline blood pressure, baseline heart rate, sensory block level, and time from anesthesia initiation to fetal delivery, did not show any significant differences between the two groups as indicated in Table 1.

The sequence number of responses to phenylephrine and norepinephrine infusion in the two groups of pregnant women is illustrated in Figure 2. The Results obtained from isotonic regression analysis revealed that the ED90 values of the phenylephrine and norepinephrine group for preventing spinal anesthesia-induced hypotension were 0.597 (95% CI: 0.582–0.628) and 0.054 (95% CI: 0.053–0.056) μg/kg/min, respectively, with an efficacy ratio of 11.1:1. The results of Probit regression analysis revealed that the ED90 values for the phenylephrine and norepinephrine groups were determined to be 0.665 (95% CI: 0.576–1.226) and 0.055 (95% CI: 0.047–0.109) μg/kg/min, respectively, with an efficacy ratio of 12.1:1. Figure 3 illustrates the dose-response curves obtained from Probit regression analysis for both groups of pregnant women in preventing spinal anesthesia-induced hypotension.

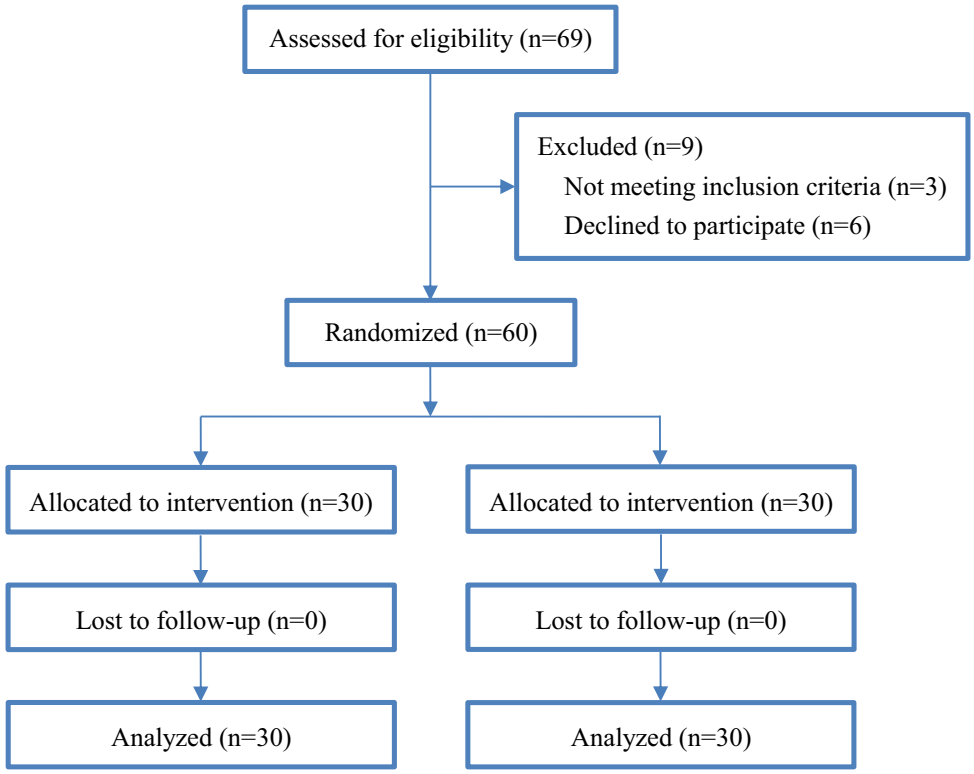

Figure 1 The Consolidated Standards of Reporting Trials flow diagram.

The incidence of maternal outcomes, including the incidence of spinal anesthesia-induced hypotension, bradycardia, nausea or vomiting, and hypertension, as well as neonatal outcomes, including umbilical artery pH and base excess values, and Apgar scores at 1 and 5 minutes did not exhibit any significant differences between two groups as indicated in Table 2.

Discussion

The results of this study demonstrated that the ED90 for preventing spinal anesthesia-induced hypotension in the norepinephrine group was 0.054 (95% CI: 0.053–0.056) μg/kg/min (isotropic regression analysis) and 0.055 (95% CI: 0.047–0.109) μg/kg/min (Probit regression analysis). The ED90 in the phenylephrine group was found to be 0.597 (95% CI: 0.582–0.628) μg/kg/min (isotropic regression analysis) and 0.665 (95% CI: 0.576–1.226) μg/kg/min (Probit regression analysis). The efficiency ratios between the two groups were calculated as approximately 11:1 and 12:1, respectively.

Table 1 Maternal Characteristics

	Phenylephrine Group (n=30)	Norepinephrine Group (n=30)	*P* value
Age, years	30.73 ± 6.20	31.17 ± 5.26	0.771
Body mass index, kg/m^2	31.19 ± 4.71	29.89 ± 4.11	0.260
Baseline systolic blood pressure, mmHg	149.27 ± 13.40	146.53 ± 13.62	0.437
Baseline diastolic blood pressure, mmHg	92.07 ± 10.27	93.00 ± 9.09	0.711
Baseline mean arterial pressure, mmHg	111.17 ± 10.25	110.83 ± 9.84	0.898
Baseline heart rate, bpm	86.03 ± 13.86	90.90 ± 14.13	0.183
Sensory block	T6 (T5 - T6)	T5 (T5 - T6)	0.181
Anesthesia to fetal delivery, min	14.60 ± 3.56	14.67 ± 2.62	0.934

Note: Values are mean ± SD or median (IQR).

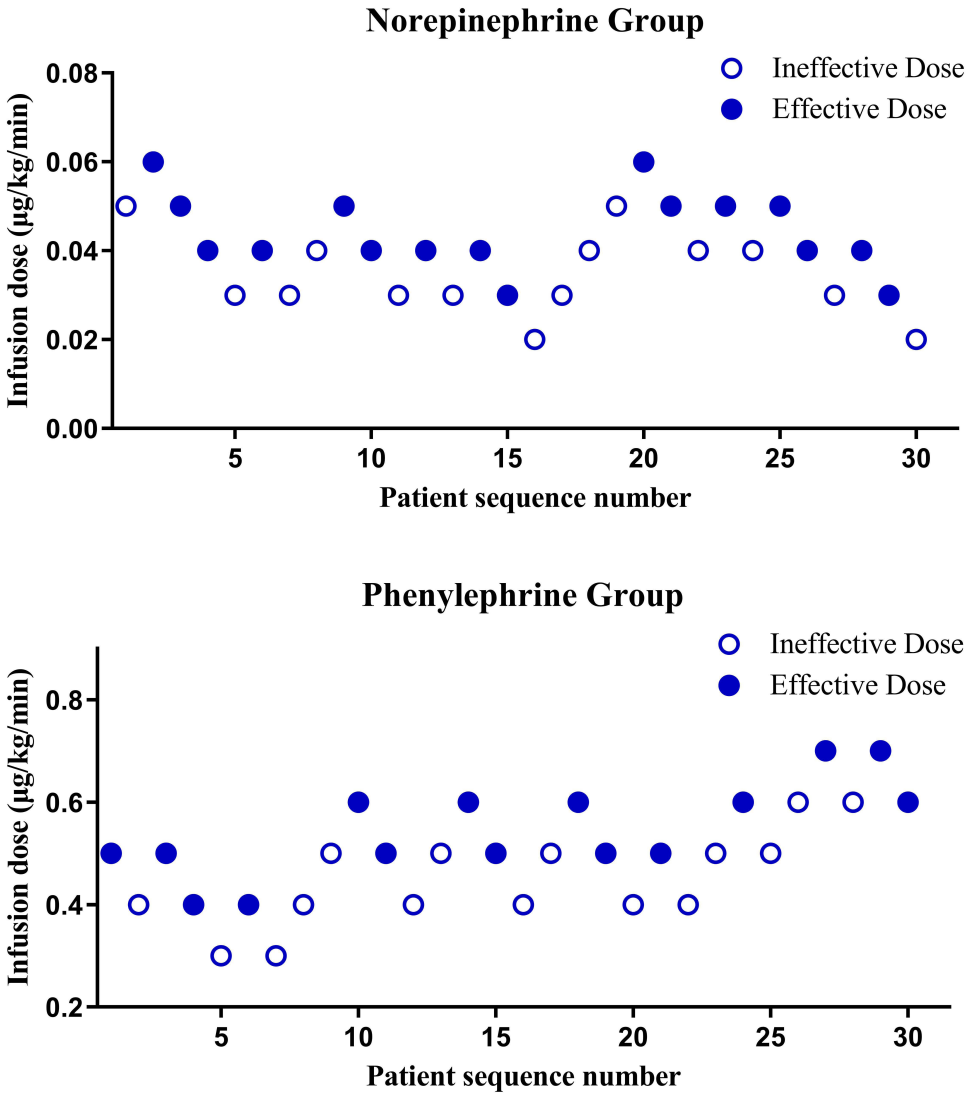

Figure 2 The sequence number of responses to phenylephrine and norepinephrine infusion in the two groups of women with preeclampsia.

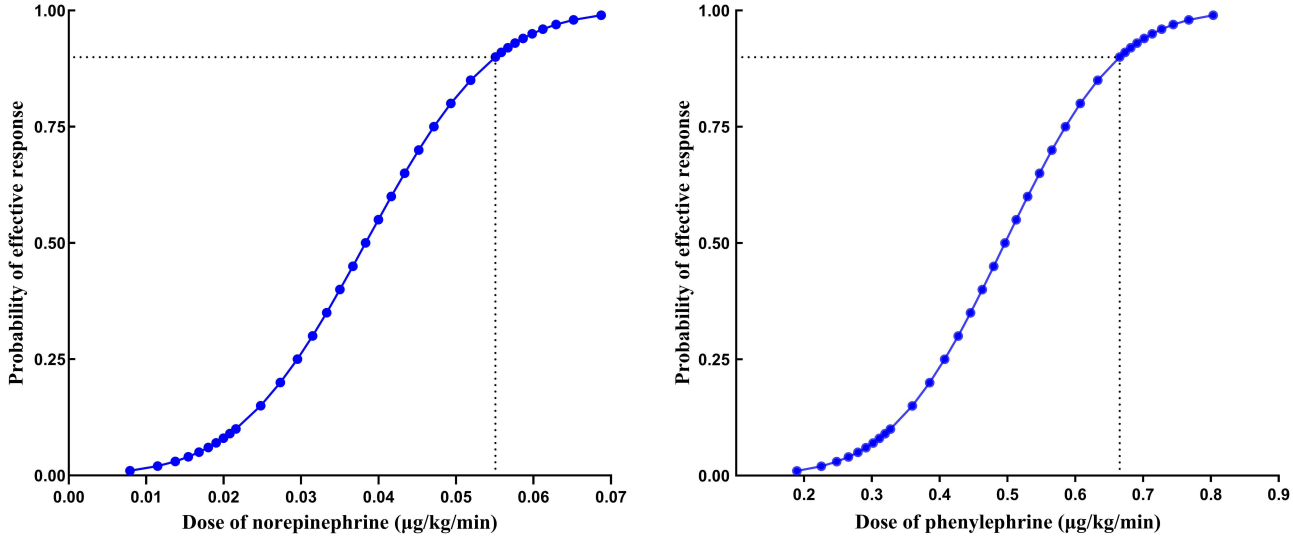

Figure 3 The dose-response curves and ED 90s (represented with the dotted lines) obtained from Probit regression analysis for both groups of women with preeclampsia in preventing spinal anesthesia-induced hypotension.

Table 2 Maternal and Neonatal Outcomes

	Phenylephrine Group (n=30)	Norepinephrine Group (n=30)	*P* value
Anesthesia induced-hypotension, n (%)	15 (50.0)	14 (46.67)	0.796
Bradycardia, n (%)	8 (26.67)	3 (10.0)	0.182
Hypertension, n (%)	2 (6.6)	1 (3.3)	0.550
Nausea or vomiting, n (%)	8 (26.67)	7 (23.3)	0.766
pH	7.31 ± 0.03	7.31 ± 0.03	0.308
Base excess (mmol/L)	−4.17 ± 1.51	−4.40 ± 1.42	0.535
Apgar score (1 min)	9 (8–9)	9 (8–9)	0.399
Apgar score (5 min)	10 (9–10)	9 (9–10)	0.800

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

In normotensive women, while spinal anesthesia is more likely to induce more severe and longer duration hypotension, timely management does not significantly impact fetal Apgar scores and outcomes.[14] Conversely, for women with preeclampsia, inadequate blood flow within the uterus-placenta interface directly affects fetal growth and development. Spinal anesthesia can cause comparatively severe and persistent hypotension in such cases, resulting in a compromised perfusion that further influences neonatal outcomes.[15,16] The increased sensitivity of women to vasopressors has raised concerns regarding the use of relatively large doses in women with preeclampsia. The previous concern was that the administration of vasopressors could potentially result in excessive vasoconstriction, thereby compromising uterine and placental perfusion and significantly elevating the risk of hemorrhagic stroke.[5] Although small bolus doses of vasopressors are commonly administered, maternal shivering and hemodynamic instability caused by spinal anesthesia can result in inaccurate blood pressure monitoring. Additionally, the delayed response time of traditional non-invasive blood pressure monitoring may hinder prompt management of spinal anesthesia-induced hypotension. Prophylactic infusion is widely utilized in normotensive pregnant women as it offers the advantage of ensuring more stable maternal hemodynamics without necessitating specific attention to the aforementioned influencing factors.[17] It is of greater significance to explore the optimal dosage of vasopressors that can effectively elevate blood pressure in women with preeclampsia, without over-correcting and increasing the risk of adverse events.

The prophylactic use of phenylephrine and norepinephrine in women with preeclampsia has received limited research attention. The initial doses of phenylephrine and norepinephrine at 0.5 and 0.1 μg/kg/min, respectively, were administered to normotensive pregnant women using an up-and-down sequence allocation method in a study conducted by Qian et al.[12] The objective was to maintain systolic blood pressure within ± 20% of baseline level. The ED90 values for phenylephrine and norepinephrine were determined as 0.449 (95% CI: 0.390–0.679) and 0.080 (95% CI: 0.069–0.120), respectively, resulting in an efficacy ratio of 5.68:1. The study conducted by Jin et al[18] compared different doses of norepinephrine infusion (0.02, 0.04, 0.06, 0.08, and 0.1 μg/kg/min) in combination with either a crystalloid or colloid co-load for the prevention of spinal anesthesia-induced hypotension. The results showed that the ED90 values were estimated to be 0.097 (95% CI: 0.072–0.157) and 0.070 μg/kg/min (95% CI: 0.053–0.107), respectively, indicating that the colloid group required approximately a 30% lower dose of norepinephrine infusion compared to the crystalloid group. The study conducted by Guo et al[19] compared the infusion of different doses of norepinephrine (NS, 0.025, 0.05, 0.075 and 0.1 μg/kg/min) in combination with a 500 mL colloid for the prevention of spinal anesthesia-induced hypotension during spinal anesthesia. The results revealed that the ED90 of norepinephrine was determined to be 0.081 (95% CI: 0.063–0.119) μg/kg/min. The study conducted by Xiao et al[20] demonstrated that the administration of phenylephrine at doses of 0.25, 0.375, 0.5, or 0.625 μg/kg/min effectively prevented spinal anesthesia-induced hypotension. The ED90 was determined to be 0.54 (95% CI: 0.46–0.76) μg/kg/min. The prophylactic infusion of phenylephrine was compared with NS at rates of 25, 50, 75, and 100 μg/min by Allen et al.[21] The incidence of pre-delivery hypotension was found to be 80%, 30%, 15%, 11%, and 0% for the respective infusion rates. Using Probit regression analysis with a hypothetical maternal body weight of 80kg, the estimated ED90 for preventing spinal anesthesia-induced hypotension in this study was determined to be 0.904 μg/kg/min. It should be noted that the ED90 values reported above for

phenylephrine and norepinephrine in preventing spinal anesthesia-induced hypotension in normotensive hypertensive women were higher than those observed in women with preeclampsia in our study. Nikooseresht et al[5] demonstrated that pregnant women with preeclampsia exhibit a reduced occurrence of hypotension and require fewer vasopressors for the restoration of maternal blood pressure compared to normotensive pregnant women. These individuals are able to effectively maintain vascular tone due to pronounced vasoconstriction, thereby limiting the decline in mean arterial pressure.[22] The dosage of vasopressors needed is lower than that required by normotensive women.

The initial application of phenylephrine and norepinephrine in the prevention of spinal anesthesia-induced hypotension during obstetric anesthesia utilized an efficacy ratio of 20:1, demonstrating that both norepinephrine at a concentration of 5 μg/mL and phenylephrine at a concentration of 100 μg/mL, with an initial dosage rate of 30 mL/h for both vasopressors, effectively maintained maternal blood pressure.[23] Subsequently, the same research team employed a random-allocation graded dose-response study to determine that the efficacy ratio between phenylephrine (60–200 μg) and norepinephrine (4–12 μg) was approximately 13.1:1.[24] Subsequently, Mohta et al[25] implemented rescue measures to address spinal anesthesia-induced hypotension by initiating a dosage of 100 μg phenylephrine and 6 μg norepinephrine, with incremental or decremental adjustments of 10 μg and 0.5 μg bolus. The ED95 values were determined to be 43.1 μg (95% CI: 39.5–65.0) for phenylephrine and 3.7 μg (95% CI: 3.5–4.7) for norepinephrine, resulting in an efficacy ratio of approximately 11.3:1 (95% CI: 8.1–16.9). In our study, isotonic regression analysis and Probit regression analysis yielded efficacy ratios of approximately 11.1:1 and 12.1:1 respectively, demonstrating consistent findings with the aforementioned literature.

Due to the increased fluid sensitivity in women with preeclampsia, vasopressors are more effective in maintaining maternal cardiac output and arterial blood pressure compared to fluid therapy.[26] Currently, both preventive and rescue phenylephrine and norepinephrine have demonstrated efficacy in preventing spinal anesthesia-induced hypotension without increasing adverse events for pregnant women. Norepinephrine has consistently been considered a viable alternative to phenylephrine, as it maintains better cardiac output and heart rate while not impacting neonatal outcomes.[27,28] The study conducted by Sharkey et al[29] compared the administration of 6 μg norepinephrine or 100 μg phenylephrine for the prevention of spinal anesthesia-induced hypotension. The results revealed a significantly reduced incidence of maternal bradycardia in the group receiving norepinephrine (10.9% vs 37.5%; $P < 0.001$). Furthermore, the requirement for treatment of spinal anesthesia-induced hypotension was significantly lower in the norepinephrine group with bolus ephedrine intervention (7.2% vs 21.4%; $P < 0.03$). The study conducted by Belin et al[30] compared the administration of preventive doses of phenylephrine at a rate of 0.5 μg/kg/min and norepinephrine at a rate of 0.05 μg/kg/min to maintain maternal systolic blood pressure above 90% of the baseline level. The group that received norepinephrine infusion demonstrated better maintenance of maternal cardiac index (90–100% vs 81–88%, $P = 0.001$), a lower proportion with assessed maternal blood pressure < 65 mmHg (0.5% vs 2.9%; $P = 0.012$), and a reduced incidence of systolic blood pressure < 80% of the baseline level (2.3% vs 8.5%; $P = 0.006$). The prophylactic infusion of norepinephrine at a dose of 0.05 μg/kg/min and phenylephrine at a dose of 0.1 μg/kg/min were compared by Vallejo et al.[31] They found that the number of patients requiring rescue bolus in both groups was similar. However, the phenylephrine group had a higher frequency of ≥ 1 dose of ephedrine (23.7% vs 2.3%; $P < 0.01$) and a higher incidence of nausea (26.3% vs 16.3%; $P < 0.001$) compared to the norepinephrine group. Other indicators such as cardiac output, cardiac index, stroke volume showed no significant differences between the two groups.

In this study, effectively evaluating the effects of phenylephrine and norepinephrine on maternal and neonatal outcomes under different prophylactic infusion doses using the up-and-down sequence allocation method poses challenges. However, our findings indicate that both vasopressors yield similar maternal and neonatal outcomes. Firstly, as catecholamines, phenylephrine and norepinephrine exhibit comparable efficacy. Despite varying efficacy ratios reported in previous studies, they are equally effective in managing spinal anesthesia-induced hypotension in women with normotension or preeclampsia.[32] Second, although ephedrine has not been demonstrated to significantly elevate the risk of neonatal acidemia in women with preeclampsia and does not further diminish maternal pH and BE, its heightened potential for fetal metabolic acidemia across the placental barrier raises concerns in women already experiencing severe placental malperfusion.[33,34] Furthermore, catecholamines such as phenylephrine and norepinephrine have an advantage over ephedrine due to their degradation within the placenta.

There are still some limitations in this study. Firstly, the up-and-down sequence allocation method can effectively calculate the ED90 of vasopressor administration with a reduced sample size, but it has certain constraints when evaluating maternal and neonatal outcomes. High-quality RCT studies will provide better insights into the effects of different doses on maternal and neonatal outcomes while assessing ED90. Secondly, further research is needed to elucidate the impact of phenylephrine and norepinephrine on hemodynamics, including cardiac output and systemic vascular resistance, in women with preeclampsia. This will help clarify the influence of these vasopressors on maternal placental perfusion and neonatal outcome, facilitating a more rational application of vasopressors in such patients.

In conclusion, according to our findings, the ED90s we calculated for both phenylephrine and norepinephrine infusions were lower in the population of women with preeclampsia than in normotensive parturients. The administration of 0.05 μg/kg/min norepinephrine and 0.6 μg/kg/min phenylephrine has been found to effectively manage a 90% incidence of spinal anesthesia-induced hypotension in women with preeclampsia.

Data Sharing Statement

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

Disclosure

The authors have no conflicts of interest in this work.

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