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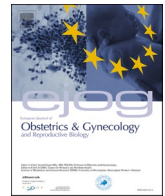
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Review article

Efficacy and safety of norepinephrine versus phenylephrine for post-spinal hypotension in preeclamptic patients: A systematic review and meta-analysis

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ABSTRACT

Objective: We conducted a systematic review and *meta-analysis* to evaluate the fetomaternal outcomes after the administration of norepinephrine or phenylephrine for the treatment of post spinal hypotension in preeclamptic women undergoing a cesarean section.**Data sources:** We searched on PubMed, Embase, Scopus, Cochrane CENTRAL, and clinicaltrials.gov from inception till June 2024.**Study selection:** Randomized controlled trials of preeclamptic women receiving norepinephrine or phenylephrine for post spinal hypotension were included.**Data extraction and synthesis:** Two reviewers extracted data onto an Excel spreadsheet. R version 4.4 was used for statistical analysis. Risk ratios (RR) and their 95% confidence intervals (CIs) were calculated and pooled using the random effects model. Cochrane's risk of bias (RoB 2) tool was used for quality assessment. This review has been registered with PROSPERO (CRD42024532740).**Results:** A total of 4 trials, comprising 413 participants, were included in this review. 206 patients received norepinephrine, while 207 received phenylephrine. The incidence of maternal bradycardia was significantly lower in the norepinephrine group compared with the phenylephrine group (RR = 0.25, 95 % CI = 0.16 to 0.39, $p < 0.01$). There were no statistical differences in other maternal outcomes or in the umbilical artery and umbilical vein blood gas analysis values. We also analyzed adverse events such as nausea (RR = 1.00, 95 % CI: 0.62 to 1.60, $p = 1.00$) and vomiting (RR = 0.99, 95 % CI: 0.89 to 1.11, $p = 0.61$), but they did not show a significant association with any group. All the trials had a moderate or low risk of bias.**Conclusion:** Bolus doses of NE and PE for the treatment of post-spinal hypotension in preeclamptic women undergoing cesarean sections were found to exhibit comparable neonatal outcomes. However, NE provided superior maternal safety due to a lower incidence of bradycardia compared to PE.

Introduction

With an incidence of 6–8 % of pregnancies, hypertension is by far the most frequent maternal health issue [1]. Preeclampsia, a pregnancy-

specific hypertensive condition, manifests itself after the 20th week of gestation and is marked by high blood pressure and proteinuria [1]. While maternal mortality rates are particularly elevated in developing nations, preeclampsia and its associated complications remain among

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the leading causes of mother deaths, even in developed countries [2]. The pathophysiology of preeclampsia is characterized by abnormal placentation and impaired trophoblast growth, compromised placental angiogenesis, and an elevated systemic inflammatory response in the mother [1]. Unmanaged hypertension significantly raises the mother's chances of experiencing heart failure, cerebral vascular events, and renal failure. It can also lead to restricted fetal growth, premature births, and stillbirths [3].

The choice of medication for treating preeclampsia depends on various aspects, such as the severity of symptoms, the presence of maternal or fetal complications, the risk of developing eclampsia, the stage of pregnancy, and the condition of the cervix. The clinician must also consider the medications' teratogenic potential and lactation safety [4,5]. Currently, spinal anesthesia is the preferred anesthetic method for preeclamptic women who do not have contraindications to neuraxial anesthesia [6]. However, sympathetic block following spinal anesthesia causes post-spinal anesthesia hypotension [7]. Severe hypotension might aggravate pre-existing uteroplacental hypoperfusion in preeclamptic individuals, therefore endangering the life of the fetus [7].

Existing data provide evidence for the prophylactic administration of vasopressors to mitigate the intensity of hypotension caused by spinal anesthesia [8]. Administering prophylactic phenylephrine infusions can reliably and securely prevent hypotension in patients with preeclampsia [8]. Nevertheless, it can lead to a reduction in the mother's heart rate (HR) and cardiac output (CO) while simultaneously raising blood pressure (BP) [9]. While healthy pregnant women and their fetuses can often handle these changes without any issues, a fetus that is already at risk due to severe preeclampsia may not be able to cope with a further decrease in blood flow to the uterus and placenta [9]. Because of its α -adrenergic agonist activity, Norepinephrine has recently been emphasized for treating post-spinal hypotension as an intravenous infusion or bolus. Although phenylephrine and norepinephrine may not have significant differences in efficacy, norepinephrine can reduce the occurrence of maternal bradycardia [10].

Despite the presence of several trials that investigate the efficacy of norepinephrine and phenylephrine for the management of post-spinal hypotension in patients with preeclampsia undergoing cesarean delivery [11,12,7,9], to the best of our knowledge, there has been no meta-analysis on this topic to date. Therefore, given the current literature, we decided to pool the results of the available studies that evaluate the efficacy of norepinephrine and phenylephrine in preeclampsia patients to generate an aggregated result, enhancing the generalizability and reliability of conclusions regarding norepinephrine and phenylephrine usage in the preeclamptic population.

Methods

We reported this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. The review is registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42024532740).

Data sources & search strategy

We performed an electronic search across multiple databases, including PubMed/MEDLINE, Embase, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and [ClinicalTrials.gov](https://www.clinicaltrials.gov), from inception until June 01, 2024, with no language restriction. Our search strategy utilized the following keywords and Medical Subject Headings (MeSH) terms: "Preeclampsia," "Norepinephrine," "Phenylephrine," and "Cesarean." The detailed search strategy for each database is provided in [Supplementary Table S1](#).

Eligibility criteria & study selection

The inclusion criteria included studies that i) enrolled adult patients diagnosed with preeclampsia, ii) involved patients undergoing c-sections, iii) the presence of post-spinal hypotension, iv) compared norepinephrine and phenylephrine, and v) randomized controlled trials (RCTs). We excluded studies involving irrelevant interventions. We did not include studies lacking sufficient data or those categorized as case reports, case series, or reviews.

All articles retrieved through the online search were screened, and duplicates were removed. Two authors independently reviewed the titles and abstracts during the initial screening phase. The remaining articles underwent thorough full-text screening by the same authors, and any discrepancies were resolved by consulting a third author.

Data extraction

After screening, two reviewers extracted data from the eligible studies and entered it into an Excel spreadsheet for consistency. The extracted data included the first author's last name, year of publication, total number of participants in each arm, mean age of participants, maternal standardized heart rate, which was calculated by studies by considering the average area under the curve, maternal bradycardia occurrence, maternal systolic blood pressure (SBP) at 9 min post-administration of vasopressor, neonatal weight, Apgar scores at 1 min (<7), umbilical blood gas outcomes (artery and vein), and adverse events such as nausea and vomiting. PlotDigitizer [14] was used to extract values for maternal SBP at 9 min post-administration of vasopressor.

Risk of bias assessment

The Cochrane risk-of-bias tool for randomized trials (RoB 2) was utilized to assess the quality of the included studies [15]. This tool evaluates five domains of a randomized study to determine the overall risk of bias: 1) bias in the randomization process, 2) bias due to deviations from intended interventions, 3) bias due to missing outcome data, 4) bias in outcome measurement, and 5) bias due to selective reporting of results.

Certainty of evidence

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [16]. The summary of effects table was generated using the GRADEpro Guideline Development Tool [17].

Statistical analysis

Statistical analysis was conducted on R version 4.4 using the "meta" package. We calculated the Risk Ratio (RR) and their 95 % Confidence Intervals (CIs) for dichotomous outcomes. Mean Difference (MD) and their 95 % CIs, were calculated for continuous outcomes when Mean and Standard Deviation (SD) were provided. Measures reported in different units were converted into a common unit to maintain uniformity across the studies for calculating MD. When data were provided as the median, they were converted to the mean, and the interquartile range (IQR) was converted to the standard deviation (SD) using the methods described by Luo et al. and Wan et al., respectively [18,19]. Skewed data were excluded from the analysis [20]. The RRs with 95 % CIs were pooled utilizing the Mantel-Haenszel method within a random effects model, while the mean differences (MDs) were combined using the inverse variance method [21]. To account for potential statistical heterogeneity, the Knapp-Hartung adjustment was applied to the confidence intervals [22]. The variance was determined using the Paule-Mandel estimator for dichotomous outcomes and the restricted maximum likelihood

estimator for continuous outcomes [23,24]. Heterogeneity was evaluated in accordance with the threshold values outlined in the Cochrane Handbook for Systematic Reviews of Interventions for the Higgins I² statistic, considering the results of the Chi² test [25]. We assessed Publication Bias through the 'metasens' package of R for Doi plots and the Luis-Furuya Kanamori index. The LFK index possesses greater sensitivity and statistical power compared to the Egger test, making it more appropriate for analyses involving less than ten studies [26]. We reported prediction intervals to report where the results of future studies might lie [27]. Sensitivity analysis through the leave-one-out (L1O) method was done whenever there were more than two studies for an outcome. P-value < 0.05 was considered statistically significant for all outcomes.

Results

Characteristics of included studies

A total of 4 RCTs [11,12,7,9] were included in this systematic review and meta-analysis after thorough search and screening (Fig. 1). A total of 413 participants were included in our review, out of which 206 received norepinephrine while 207 received phenylephrine. The mean age of the participants ranged from 26.5 years to 32.5 years. All studies employed intrathecal administration of spinal anesthesia [11,12,7,9]. Table 1 outlines the characteristics of the studies included in this review. The

Doi plots for patients with an event of bradycardia and umbilical arterial pCO₂ did not reveal asymmetry (Supplementary Fig. F1 and F2), whereas that for nausea revealed minor asymmetry (Supplementary Fig. F3). The Doi plots revealed major asymmetry for all other outcomes, as observed in Supplementary Fig. F14–F17.

Risk of bias assessment

Wang et al. [11] was deemed to have a low risk of bias, whereas there were some concerns for the rest of the studies [7,9,12] included in our review (Supplementary Fig. F18 and F19).

Maternal outcomes

Incidence of maternal bradycardia was significantly lower with the use of norepinephrine (RR: 0.25, 95 % CI: 0.16 to 0.39, p-value < 0.01; I² = 0 %, Fig. 2; high certainty of evidence, Table 2). However, standardized heart rate was not significantly associated with the use of either vasopressor (MD: 4.28 bpm, 95 % CI: –1.88 to 10.44, p-value = 0.07; I² = 0 %, Supplementary Fig. 20; low certainty of the evidence, Table 2). Furthermore, the value of maternal SBP at 9 min was not significantly different with the use of either norepinephrine or phenylephrine (MD: –3.78 mmHg, 95 % CI: –8.25 to 0.69, p-value = 0.07; I² = 0 %, Supplementary Fig. 21; low certainty of the evidence, Table 2).

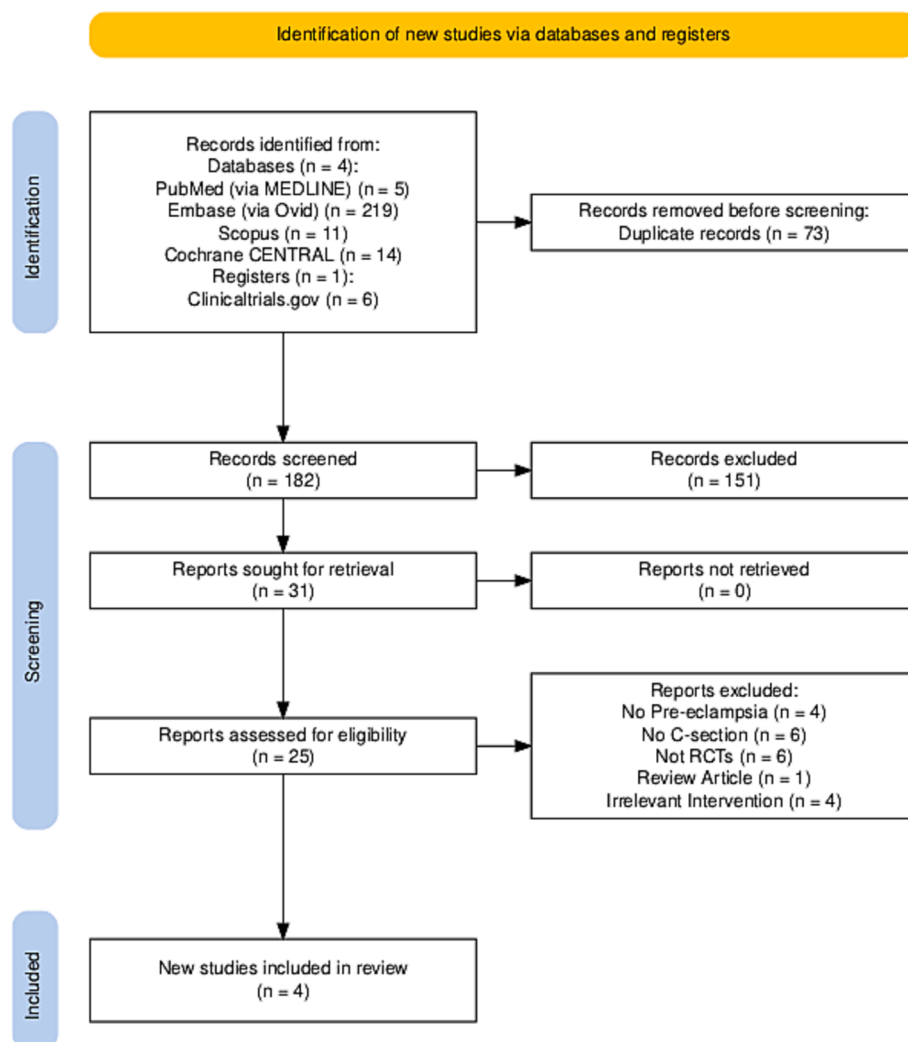


Fig. 1. PRISMA flow diagram.

Table 1
Baseline characteristics of included studies.

Baseline Characteristics		Guo et al. 2022	Mohta et al. 2021	Wang et al. 2019	Pan et al. 2014
Country		China	India	China	China
Participants (n)	I	69	43	56	39
	C	69	43	55	39
Intervention (I)		0.05 µg kg ⁻¹ min ⁻¹ Norepinephrine	4 µg ml ⁻¹ Norepinephrine	4 µg Norepinephrine	4.5 µg Norepinephrine
Control (C)		0.625 µg kg ⁻¹ min ⁻¹ Phenylephrine	50 µg ml ⁻¹ Phenylephrine	50 µg Phenylephrine	60 µg Phenylephrine
Age in years (mean ± SD)	I	32 (20–43) *	26.5 ± 4.6	32 ± 4.1	32.5 ± 4.5
	C	31 (18–44) *	27.0 ± 4.4	32 ± 4.4	31.7 ± 4.2
Weight in kilograms (mean ± SD)	I	N/A	71.2 ± 8.0	76.5 ± 8.1	75.3 ± 11.6
	C	N/A	72.0 ± 10.0	78.5 ± 9.2	75.4 ± 10.0
Height in centimeters (mean ± SD)	I	N/A	155.0 ± 4.9	162 ± 5.1	159.4 ± 5.6
	C	N/A	155.9 ± 4.4	162 ± 4.7	159.9 ± 5.7
Gestation period in weeks (median-IQR)	I	37 (35–38)	38 (36–39)	274 ± 9† days	37.1 (34.0–38.0)
	C	36 (34–38)	37 (36–39)	273 ± 12† days	37 (34.0–38.6)
Block height (thoracic dermatome) (median-IQR)	I	6 (5–6)	5 (4–6)	At 5 min = 5 (5–6) At 15 min = 4 (3–5)	5 (4–6)
	C	6 (5–6)	5 (5–6)	At 5 min = 5 (5–6) At 15 min = 4 (4–4)	5 (4–6)

I = Intervention, C = Control, SD = Standard deviation, *=median (range), †=mean ± SD, IQR = Interquartile range

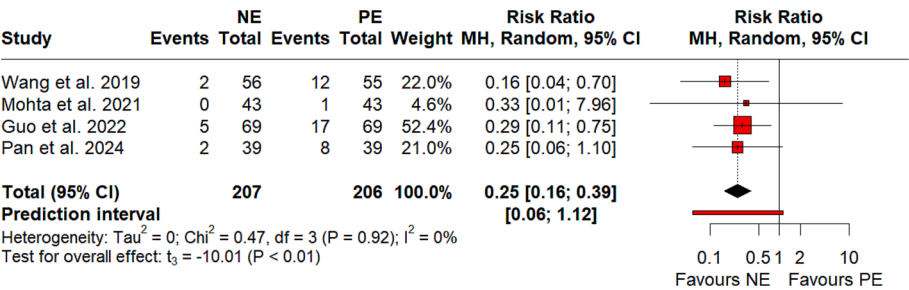


Fig. 2. Forest plot of patients with an event of bradycardia.

Neonatal outcomes

The weight of the neonate delivered was not significantly associated with the use of either vasopressor (MD: 0.00, 95 % CI: -0.86 to 0.86, p-value = 0.97; I² = 0 %, [Supplementary Fig. 22](#); low certainty of evidence, [Table 2](#)). Similarly, the risk of Apgar scores being less than 7 at 1 min was not significantly associated with the use of either vasopressor (RR: 0.82, 95 % CI: 0.26 to 2.63, p-value = 0.27; I² = 0 %, [Supplementary Fig. 23](#); low certainty of evidence, [Table 2](#)).

Umbilical artery blood gas analysis

The use of either norepinephrine or phenylephrine did not result in a statistically significant difference in the pH (MD: 0.00, 95 % CI: -0.00 to 0.01, p-value = 0.64; I² = 0 %, [Fig. 3\(a\)](#); low certainty of the evidence, [Table 2](#)).

Similar results were observed for other variables including pO₂ observed in the umbilical artery blood gas analysis (MD: 0.64 mmHg, 95 % CI: -1.35 to 2.63, p-value = 0.38; I² = 5 %, [Fig. 3\(b\)](#); low certainty of the evidence, [Table 2](#)), pCO₂ (MD: 0.41 mmHg, 95 % CI: -1.11 to 1.92, p-value = 0.45; I² = 0 %, [Fig. 3\(c\)](#); moderate certainty of the evidence, [Table 2](#)), HCO₃⁻ (MD: -0.33 mmol/L, 95 % CI: -0.10 to 0.75, p-value = 0.08; I² = 0 %, [Fig. 3\(d\)](#); low certainty of evidence, [Table 2](#)), and base excess (MD: -0.06 mmol/L, 95 % CI: -1.03 to 0.91, p-value = 0.85; I² = 39 %, [Fig. 3\(e\)](#); low certainty of evidence, [Table 2](#)) in the umbilical artery blood gas analysis, all of which showed no significant association with the use of either vasopressor.

Umbilical vein blood gas analysis

In the blood gas analysis of the umbilical vein, the use of either vasopressor did not yield a significant difference in the measured pH (MD: -0.01, 95 % CI: -0.06 to 0.05, p-value = 0.36; I² = 0 %, [Fig. 4\(a\)](#); low certainty of evidence, [Table 2](#)).

Moreover, the pO₂ (MD: 3.96, 95 % CI: -62.51 to 70.43, p-value = 0.59; I² = 89 %, [Fig. 4\(b\)](#); very low certainty of the evidence, [Table 2](#)), pCO₂ (MD: -0.16, 95 % CI: -28.79 to 28.46, p-value = 0.95; I² = 75 %, [Fig. 4\(c\)](#); very low certainty of the evidence, [Table 2](#)), HCO₃⁻ (MD: 0.30, 95 % CI: -9.00 to 9.60, p-value = 0.75; I² = 65 %, [Fig. 4\(d\)](#); very low certainty of the evidence, [Table 2](#)), and base excess (MD: 0.30, 95 % CI: -2.33 to 2.92, p-value = 0.38; I² = 0 %, [Fig. 4\(e\)](#); low certainty of the evidence, [Table 2](#)) values of the umbilical vein blood gas analysis were statistically associated with neither norepinephrine nor phenylephrine.

Maternal adverse events

The risk of occurrence of nausea in a patient was not significantly associated with the use of either norepinephrine or phenylephrine (RR: 1.00, 95 % CI: 0.62 to 1.60, p-value = 1.00; I² = 0 %, [Supplementary Fig. 24](#); low certainty of evidence, [Table 2](#)). Additionally, the use of either vasopressor did not pose a significant risk of the occurrence of vomiting (RR: 0.99, 95 % CI: 0.89 to 1.11, p-value = 0.61; I² = 0 %, [Supplementary Fig. 25](#); low certainty of evidence, [Table 2](#)).

Sensitivity analysis and subgroup analysis

L10 analysis for umbilical arterial pO₂, pCO₂, pH, HCO₃⁻, and base excess did not yield significant results, omitting any of the studies

Table 2
GRADE Assessment of certainty of evidence.

Outcomes	Anticipated absolute effects* (95 % CI)		Relative effect (95 % CI)	N ² of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Phenylephrine	Risk with Norepinephrine				
Maternal Bradycardia	184 per 1,000	46 per 1,000 (30 to 72)	RR 0.25 (0.16 to 0.39)	413 (4 RCTs)	⊕⊕⊕⊕High	Norepinephrine results in a reduction in maternal bradycardia.
Systolic Blood Pressure at 9 min post-administration of vasopressor		MD 3.78 mmHg lower (8.25 lower to 0.69 higher)	—	319 (3 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in Systolic Blood Pressure.
Maternal Standardized Heart Rate		MD 4.28 bpm higher (1.88 lower to 10.44 higher)	—	163 (2 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in maternal standardized heart rate.
Apgar scores at 1 min < 7	64 per 1,000	52 per 1,000 (17 to 168)	RR 0.82 (0.26 to 2.63)	189 (2 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in Apgar scores at 1 min < 7.
Neonatal Weight		MD 0 kg (0.86 lower to 0.86 higher)	—	190 (2 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in neonatal weight.
Arterial pH		MD 0 (0 to 0.01 higher)	—	397 (4 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in arterial pH.
Arterial pO ₂		MD 0.64 mmHg higher (1.35 lower to 2.63 higher)	—	390 (4 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in arterial pO ₂ .
Arterial pCO ₂		MD 0.41 mmHg higher (1.11 lower to 1.92 higher)	—	390 (4 RCTs)	⊕⊕○○ Moderate ^b	Norepinephrine likely results in little to no difference in arterial pCO ₂ .
Arterial HCO ₃ ⁻		MD 0.33 mEq/L higher (0.1 lower to 0.75 higher)	—	252 (4 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in arterial HCO ₃ ⁻ .
Arterial base excess		MD 0.06 mmol/L lower (1.03 lower to 0.91 higher)	—	397 (4 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in arterial base excess.
Venous pH		MD 0.01 lower (0.06 lower to 0.05 higher)	—	157 (2 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in venous pH.
Venous pO ₂		MD 3.96 mmHg higher (62.51 lower to 70.43 higher)	—	157 (2 RCTs)	⊕○○○ Very low ^{a,b,c}	The evidence is very uncertain about the effect of norepinephrine on venous pO ₂ .
Venous pCO ₂		MD 0.16 mmHg lower (28.79 lower to 28.46 higher)	—	157 (2 RCTs)	⊕○○○ Very low ^{a,b,c}	The evidence is very uncertain about the effect of norepinephrine on venous pCO ₂ .
Venous HCO ₃ ⁻		MD 0.3 mEq/L higher (9 lower to 9.6 higher)	—	157 (2 RCTs)	⊕○○○ Very low ^{a,b,c}	The evidence is very uncertain about the effect of norepinephrine on venous HCO ₃ ⁻ .
Venous Base Excess		MD 0.3 mmol/L higher (2.33 lower to 2.92 higher)	—	157 (2 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in venous base excess.
Nausea	49 per 1,000	49 per 1,000 (30 to 78)	RR 1.00 (0.62 to 1.60)	413 (4 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in nausea.
Vomiting	15 per 1,000	14 per 1,000 (13 to 16)	RR 0.99 (0.89 to 1.11)	413 (4 RCTs)	⊕⊕○○ Low ^{a,b}	Norepinephrine may result in little to no difference in vomiting.

*The risk in the intervention group (and its 95 % confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95 % CI). CI: confidence interval; MD: mean difference; RR: risk ratio

Explanations

- a. Doi plot asymmetry
- b. 95 % Confidence interval includes no effect
- c. High heterogeneity

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

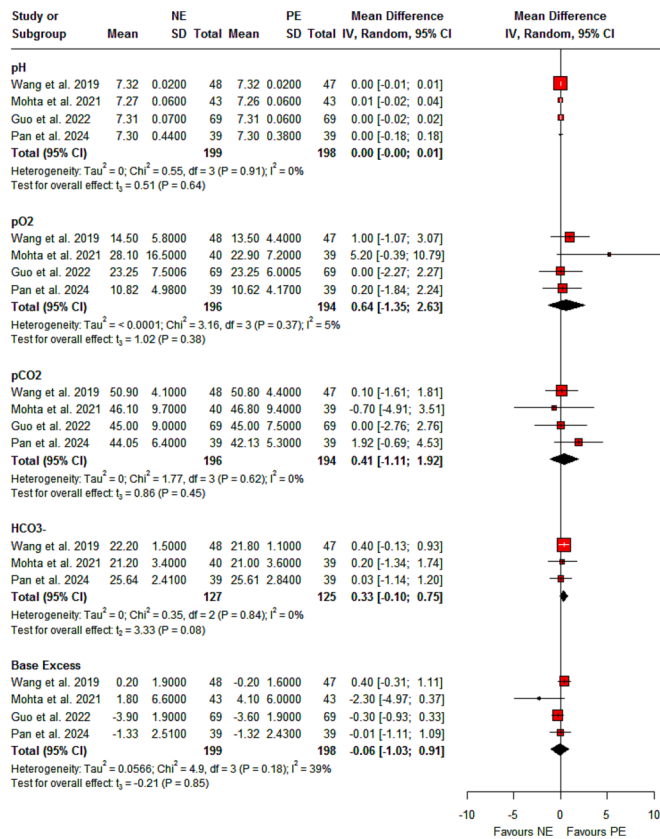


Fig. 3. Forest plot of umbilical arterial blood gas analysis (a) pH, (b) pO₂, (c) pCO₂, (d) HCO₃⁻, and (e) base excess.

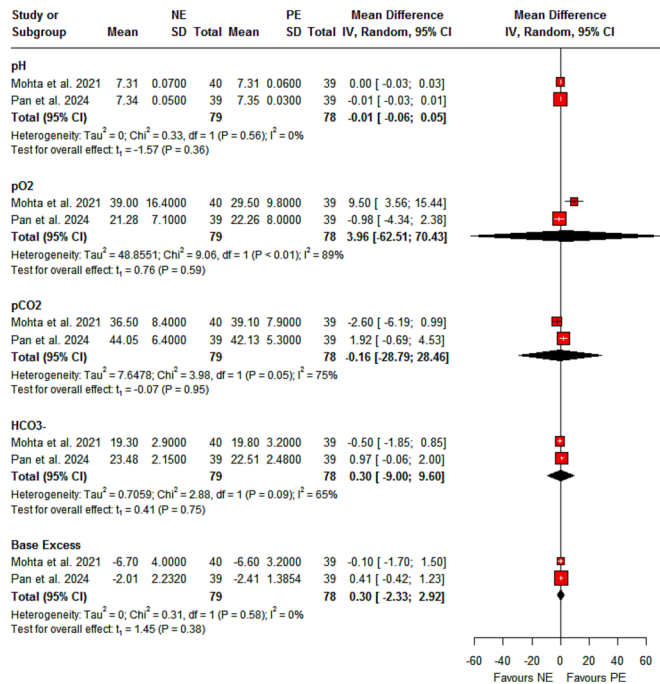


Fig. 4. Forest plot of umbilical venous blood gas analysis (a) pH, (b) pO₂, (c) pCO₂, (d) HCO₃⁻, and (e) base excess.

(Supplementary Figs. F26–F30). Similarly, significant results were not observed with L1O for either nausea or vomiting (Supplementary Figs. F31 and F32). However, significant results were observed for

maternal standardized SBP at 9 min post-administration of vasopressor after omitting Wang et al. [11] (MD: -4.35, 95 % CI: -4.99 to -3.72, p -value = < 0.01 ; $I^2 = 0\%$, Supplementary Figs. F33). Additionally, we also conducted a subgroup analysis based on the use of vasopressor as a treatment or prophylaxis. Only 1 study [7] administered vasopressor prophylactically for hypotension, while 3 studies [11,12,9] administered vasopressor for hypotension rescue. Nevertheless, the test for subgroup differences did not yield any significant results for any outcome (Supplementary Figs. F34–F42).

Discussion

In this meta-analysis, we synthesized the cumulative evidence by comparing norepinephrine and phenylephrine during the cesarean section. Our results indicated that phenylephrine was significantly associated with a risk of maternal bradycardia as compared to norepinephrine. However, we did not observe a statistically significant benefit of using either vasopressor in other maternal and neonatal outcomes, such as maternal standardized heart rate, maternal SBP at 9 min post-administration of vasopressor, the weight of neonate post-cesarean delivery, risk of Apgar score being less than 7 at 1 min, variables in the umbilical artery and vein blood gas analysis such as pH, pO₂, pCO₂, HCO₃⁻, and base excess. The quality of evidence synthesis in our meta-analysis, as reported using GRADE assessment, was very low to high.

phenylephrine is regarded as the first-line option for the management of hypotension during cesarean delivery under spinal anesthesia [28,29]. A consensus statement recommended the use of phenylephrine, even after acknowledging that drugs with β -agonist activity, such as norepinephrine and metaraminol, may have the best profiles [29]. This recommendation was made based on the fact that there might not be enough data to support this. Our meta-analysis did not reveal a significant difference in the SBP recorded after the administration of either vasopressor, suggesting that both phenylephrine and norepinephrine had a similar benefit. However, concerns have been raised over the use of phenylephrine due to a significantly higher risk of bradycardia when compared to norepinephrine [7,9,11,30]. Our analysis revealed a similar result. The lower incidence of bradycardia has been explained due to the inherent β -agonist activity of norepinephrine, which, theoretically, might have an advantage [31].

In addition to its superiority over phenylephrine, prophylactic use of norepinephrine, in comparison to no preventive measures, has been shown to reduce the incidence of maternal hypotension in patients with preeclampsia undergoing cesarean delivery [32]. Additionally, the study did not identify a significant increase in either maternal or neonatal adverse effects. When compared to phenylephrine, our analysis did not find a significant difference in the incidence of maternal or neonatal adverse effects with the use of either vasopressor, further warranting the use of norepinephrine in the light of its advantage over phenylephrine in terms of reduction in the risk of bradycardia.

It is important to acknowledge the limitations of our meta-analysis. Firstly, the small sample size of the included studies might have led to underestimation or overestimation of the pooled results and a small number of included studies might restrict the generalizability of the included studies. Secondly, we can expect a moderate degree of variance due to the different origins of the included studies which might contribute to the between-study heterogeneity. This variance might also be influenced by a difference in patient demographics and underlying comorbidities. We accounted for this using the Paule-Mandel estimator for dichotomous outcomes and the restricted maximum likelihood (REML) estimator for continuous outcomes in our meta-analysis. Of note, REML relies on a sufficient number of included studies to accurately determine variances [33], which might constitute a limitation in our meta-analysis as the number of included studies is less than 5. Thirdly, we observed an overall lower quality of synthesized evidence in our meta-analysis, whereby the pooled results were downgraded because of inconsistency, imprecision, and publication bias. Furthermore, we

utilized prediction intervals during evidence synthesis in our review, which has its own set of limitations, such as an imprecise interval prediction in *meta-analysis* where the number of included studies is less than 5, and there is evidence of publication bias [27]. We have used the Mantel-Hanzel method for synthesizing evidence in our *meta-analysis*, which is generally considered robust, especially for a *meta-analysis* that has studies with a small sample size [34]. Future research should focus on large-scale randomized controlled trials to provide robust evidence that can aid in updating treatment guidelines.

Conclusion

The use of norepinephrine and phenylephrine in managing post-spinal hypotension during cesarean delivery in preeclamptic patients appears comparable in terms of maternal and neonatal outcomes. Our analysis indicates that norepinephrine significantly reduces the incidence of maternal bradycardia compared to phenylephrine, with similar effects on other clinical outcomes. These findings suggest that both vasopressors are safe options, highlighting the need for further studies to refine clinical guidelines and optimize management strategies for this high-risk population.

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Ethics

Not applicable.

CRediT authorship contribution statement

Shahzaib Ahmed: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Eeman Ahmad:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Eeshal Fatima:** Writing – review & editing, Writing – original draft, Methodology. **Umar Akram:** Writing – review & editing, Writing – original draft, Methodology. **Obaid Ur Rehman:** Writing – original draft, Methodology. **Arya Harikrishna:** Writing – original draft, Methodology, Investigation, Conceptualization. **Shaiza Sharif:** Writing – review & editing, Methodology, Investigation. **Noreen Akmal:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Abdulqadir J. Nashwan:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejogrb.2024.10.012>.

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