Systematic Review and Meta-Analysis

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# Efficacy and safety of norepinephrine versus phenylephrine for the management of maternal hypotension during cesarean delivery with spinal anesthesia

## A systematic review and meta-analysis

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**Abstract**

**Background:** Phenylephrine is the current "gold standard" vasopressor used to treat maternal hypotension in women undergoing cesarean delivery with spinal anesthesia. Since 2015, various studies have explored the use of norepinephrine to manage maternal hypotension. We conducted this systematic review and meta-analysis of available randomized controlled trials (RCTs) to compare the efficacy and safety of norepinephrine and phenylephrine for the prevention and treatment of maternal hypotension.

**Methods:** A systematic literature search was conducted using electronic databases, including PubMed, MEDLINE, Embase (Embase.com), and the Cochrane CENTRAL register of controlled trials. Parturients underwent cesarean delivery with spinal anesthesia and received norepinephrine to prevent or treat hypotension were considered. Maternal outcomes, including incidences of hypotension, hypertension, bradycardia, intraoperative nausea and vomiting (IONV), maternal cardiac output (CO), and blood pressure (BP) control precision, as well as neonatal Apgar scores and umbilical cord blood analyses, were compared between groups.

**Results:** Three RCTs in 4 reports published between 2015 and 2018 were finally identified with a total of 294 parturients. We found there was no difference in effectiveness between norepinephrine and phenylephrine for the treatment of maternal hypotension (odds ratio [OR] 0.64; 95% confidence interval [CI] 0.37–1.10, $P = .11$), and there was no difference in the occurrence of hypertension (OR 0.74; 95% CI 0.33–1.62, $P = .45$). Of note, compared to the phenylephrine group, parturients in the norepinephrine group were less likely to experience bradycardia (OR 0.29; 95% CI 0.12–0.68, $P = .005$) and IONV (OR 0.54; 95% CI, 0.29–0.99, $P = .04$). Further, we did not observe a difference between the two vasopressors in the incidence of neonatal Apgar scores $< 7$ at 1 and 5 minutes or in umbilical vein (UV) blood gas. However, evidence is insufficient to draw conclusions regarding the greater maternal CO and better BP control precision with the use of norepinephrine.

**Conclusion:** This systematic review and meta-analysis shows norepinephrine provides similar efficacy to manage maternal hypotension compared to phenylephrine; additionally, showing advantage regarding certain side effects like bradycardia and IONV reduction. Accordingly, norepinephrine is a promising alternative to phenylephrine. However, before routine clinical application, more studies are warranted.

**Abbreviations:** BP = blood pressure, CI = confidence interval, CO = cardiac output, GRADE = grading of recommendation, assessment, development, and evaluation, HR = heart rate, IONV = intraoperative nausea and vomiting, MDAPE = median absolute performance error, MDPE = median performance error, OR = odds ratio, PICO = problem or population, interventions, comparison and outcome, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized controlled trial, RD = risk difference, SVR= systematic vascular resistance, UA= umbilical artery, UV= umbilical vein, WMD = weighted mean difference.

**Keywords:** efficacy, meta-analysis, norepinephrine, phenylephrine, safety, systematic review

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## 1. Introduction

Maternal hypotension is a physiological response during cesarean delivery with spinal anesthesia that significantly contributes to adverse maternal outcomes such as nausea, vomiting, dizziness, and even cardiovascular collapse. In addition, compromised placental perfusion raises the concerns of fetal acidosis, hypoxia, and postnatal neurological injury. Thus, the effective prevention and treatment of maternal hypotension is of great clinical significance. At present, phenylephrine is the first-line vasopressor used to manage maternal hemodynamics,[1] and the efficacy and safety of its use in this context have been comprehensively explored with regard to different dosing regimens and maintenance modes.[2,3]

However, as it is a sympathomimetic amine, phenylephrine is a pure α-adrenergic receptor agonist with little β-adrenergic receptor activity. It induces arteriolar vasoconstriction to increase systemic vascular resistance and mean blood pressure. Meanwhile, in venous capacitance vessels, similar vasoconstriction may increase venous return; however, venous resistance increases as well, thus limiting venous return to the heart.[4] An increase in blood pressure reflexively leads to a dose-dependent decrease in heart rate (HR), which leads to a decrease in cardiac output (CO).[5] This raises concerns of endangering the mother and fetus in circumstances such as uteroplacental insufficiency or fetal distress.

In recent years, norepinephrine, another traditionally used vasopressor, has attracted increased attention due to its feasibility as a substitute for phenylephrine. Norepinephrine has little β-receptor agonist activity other than its α-receptor agonism property. Theoretically, it is less likely to decrease HR and CO, which renders it a promising alternative for phenylephrine. Results of several trials suggest norepinephrine is effective for the prevention and treatment of hypotension during spinal anesthesia, and no obvious maternal or neonatal side effects have been observed.[6–8]

Therefore, we performed a systematic review and meta-analysis of eligible randomized controlled trials (RCTs) to compare the efficacy and safety of norepinephrine and phenylephrine in parturients undergoing cesarean delivery with spinal anesthesia. Our aim was to assess whether norepinephrine and phenylephrine differ in their effectiveness for the treatment of maternal hypotension and in their risks for adverse maternal and neonatal outcomes.

## 2. Methods

### 2.1. Literature search

The application of norepinephrine to prevent or treat maternal hypotension is a recent advancement, and literature regarding its use is still limited. In 2015, Kee et al[9] first reported the use of norepinephrine in obstetric anesthesia. Therefore, a systematic literature search was performed from January 1, 2015 to August 30, 2018 using PubMed, MEDLINE, Embase (Embase.com), and the Cochrane CENTRAL register of controlled trials. The following medical subject headings and keywords were used: "norepinephrine AND phenylephrine" AND "obstetric anesthesia OR cesarean section OR cesarean delivery" AND "spinal anesthesia" AND "maternal hypotension OR maternal hemodynamic." In addition, reference lists of the retrieved papers and reviews relating to vasopressors used during spinal anesthesia were screened to minimize possible omissions. There was no language restriction for the literature search. This study was approved by the Clinical Research Ethics Committee of Nanjing Medical University, Nanjing, China.

### 2.2. Inclusion criteria

We used the problem or population, interventions, comparison and outcome (PICO) framework[10] to explore the effects of norepinephrine vs phenylephrine in treating maternal hypotension during cesarean delivery with spinal anesthesia:

*Population*: Women scheduled to receive spinal anesthesia for elective or emergency cesarean delivery were considered, irrespective of normotensive or pre-eclamptic status.

*Interventions*: Norepinephrine could be administered before, during, or after the induction of spinal anesthesia to prevent or treat maternal hypotension. All dosing regimens and administration paradigms were included.

*Comparison*: Phenylephrine was used in the same setting as norepinephrine.

Outcome: The efficacy of vasopressors was the primary outcome, including the incidences of hypotension, hypertension, maternal CO, and blood pressure (BP) control precision. The safety of vasopressors was the secondary outcome, encompassing maternal intraoperative nausea and vomiting (IONV), bradycardia, neonatal Apgar scoring, and umbilical artery (UA) or umbilical vein (UV) blood gas.

### 2.3. Data extraction, risk of bias assessment, and quality of studies

We collected maternal outcomes, including the incidences of hypotension, hypertension, bradycardia, IONV, maternal CO, and BP control precision, as well as neonatal outcomes, including Apgar scores and umbilical cord blood gas. The definitions of hypotension, hypertension, and bradycardia vary among trials. We did not try to standardize them, but instead used the authors' primary definitions for our meta-analysis. Data extraction, risk of bias, and quality assessment of the eligible RCTs were performed independently by 2 authors. Discrepancies were resolved through discussion or by contacting the corresponding authors for more details.

Risk of bias was assessed for each RCT using the Cochrane Collaboration risk of bias table[10]; each was divided into 3 categories: low, unclear, or high risk. In addition, quality was evaluated based on the grading of recommendation, assessment, development, and evaluation (GRADE) Quality Assessment Checklist,[11] which takes into account risk of bias, inconsistency, indirectness, imprecision, and reporting bias.

### 2.4. Statistical analysis

Statistical analysis was performed using RevMan 5.3 (Cochrane Library Software, Oxford, UK) and STATA 15.1 software (STATA Corporation, College Station, TX). For dichotomous data, odds ratio (OR), risk difference (RR), and their 95% confidence intervals (CIs) were calculated as effect size, while weighted mean difference (WMD) with 95% CI was obtained for continuous variables. The means and standard deviations (SDs) were estimated with the method established by Hozo et al[12] in the trials where median (interquartile, IQR) were used. Forest plots were drawn to show the point estimates of each trial in relation to the pooled results. The heterogeneity test was based on the $Q$ and $I^2$ statistic. In this study, $P < .05$ or $I^2 > 50\%$ indicated heterogeneity among trials when the random-effects model

followed. Otherwise, the fixed-effects model was applied. If heterogeneity was noted ($P < .05$ and $I^2 > 50\%$), a meta-regression analysis was conducted to explore the origin of heterogeneity. Begg's funnel plot was employed using STATA 15.1 software to detect publication bias.

## 3. Results

### 3.1. Trials included

Four reports were finally enrolled in this systematic review[9,13–15]; a detailed preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart is shown in Figure 1. Of note, data from Kee et al[9] in 2015 was reanalyzed by the same study group in 2017.[14] The former explored maternal CO, systematic vascular resistance (SVR), HR, and maternal and neonatal adverse outcomes related to norepinephrine and phenylephrine, while the 2017 study[14] mainly focused on BP control precision. Therefore, there were actually 3 RCTs with a total of 294 parturients finally enrolled, including a norepinephrine group with 148 cases and a phenylephrine group with 146 cases. The mode of norepinephrine and phenylephrine administration varied among trials and included intermittent bolus,[15] fixed rate infusion,[13] or closed-loop feedback computer-controlled infusion.[9,14] In all trials, both vasopressors were used for the prevention[9,13,14] and treatment[15] of hypotension and were administered immediately post spinal anesthesia until delivery (Table 1).

### 3.2. Patients characteristics

Subjects in all eligible trials were healthy women at term with a singleton pregnancy scheduled for elective cesarean delivery. All trials used a single spinal anesthesia with bupivacaine + fentanyl[9,14] or bupivacaine + fentanyl + morphine.[13,15] Rapid cohydration was started simultaneously with intrathecal injection, and all parturients were placed in a left-tilt supine position post spinal anesthesia.

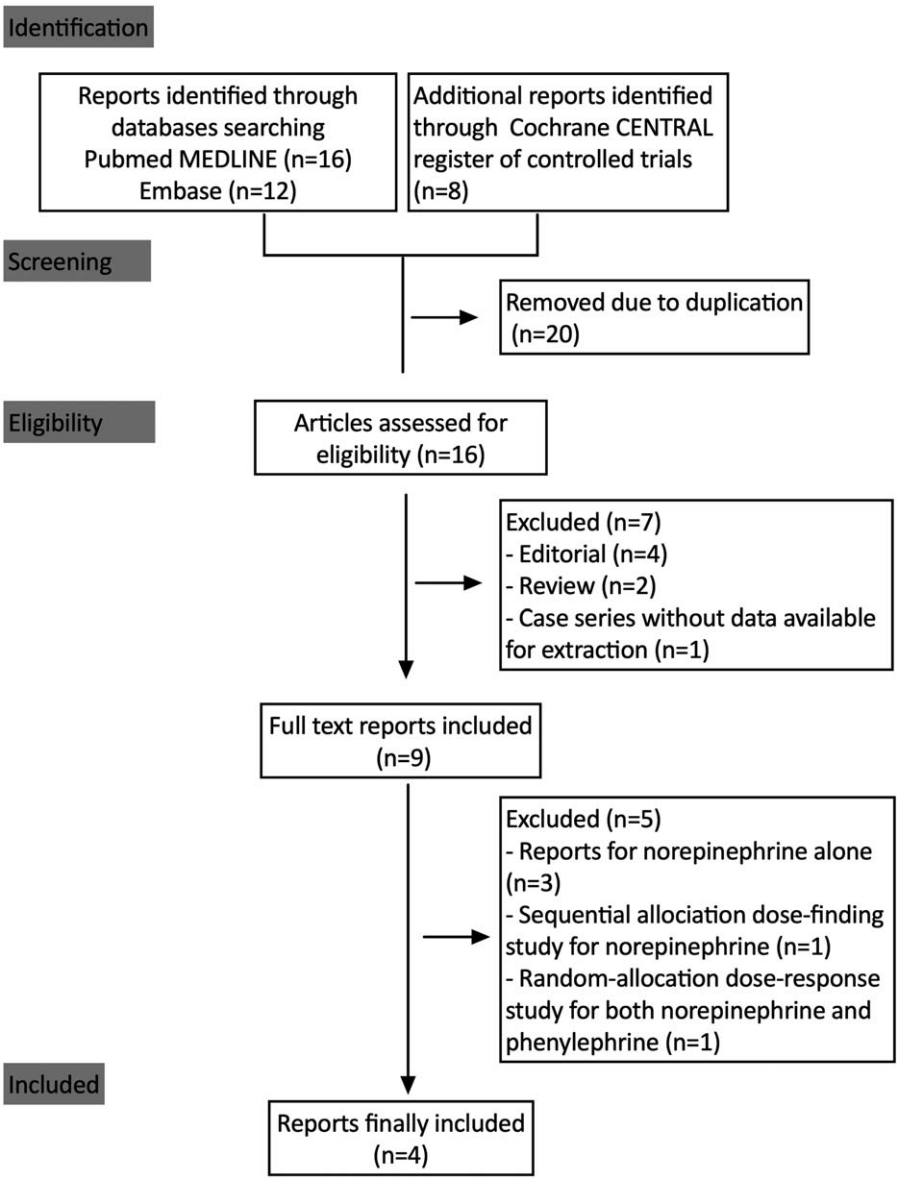


**Figure 1.** PRISM flowchart of studies enrollment.

**Table 1**

**Characteristics of included RCTs.**

| Study | Participants | Anesthesia | Mode of administration | Intervention | Outcomes |
|---|---|---|---|---|---|
| Sharkey 2018, Canada [15] | 112 Healthy women | Spinal anesthesia with bupivacaine 13.5 mg + fentanyl 10 μg+ morphine 100 μg, rapid hydration with LR for 10 mL/kg post spinal anesthesia, left tilt supine position | Intermittent bolus | NE bolus 6 μg vs PE 100 μg whenever SBP lower than baseline, ephedrine 10 mg is given when SBP < 80% baseline + HR < 60 bpm or SBP < 80% baseline for 2 consecutive readings | Incidence of hypotension (SBP < 80% baseline), hypertension (SBP > 120% baseline), bradycardia (HR < 50bpm), tachycardia (HR > 120% baseline), IONV, Apgar scoring, UA and UV blood gas |
| Kee 2017, Hong Kong [14] | 101 Healthy women | Spinal anesthesia with bupivacaine 11 mg + fentanyl 15 μg, rapid cohydration with Hartmann's solution 2 L, left tilt supine position | Closed-loop feedback computer-controlled infusion | NE 0–5 μg/min *vs* PE 0–100 μg/min for SBP near baseline with computer designed algorithm | Performance error (MDPE, MDAPE, Wobble, and divergence), incidence of hypotension (SBP < 80% baseline), hypertension (SBP > 120% baseline), bradycardia (HR < 60bpm), drug consumption |
| Vallejo 2017, USA [13] | 81 Healthy women | Spinal anesthesia with bupivacaine 12–15 mg + fentanyl 20 μg + morphine 200 μg, rapid hydration with LR 500 ml, left tilt supine position, noninvasive monitoring (Nexfin) for CO, CI, SV, SVR | Fixed rate infusion | NE 0.05 vs PE 0.1 μg/kg/min for SBP with 100–120% of baseline, rescue bolus PE 100 μg if SBP lower than baseline or ephedrine 5 mg if hypotension+bradycardia (HR < 60bpm) | Number and type of rescue bolus; maternal HR, CO, SV, CI, SBP, DBP, SVR; incidence of bradycardia (HR < 60bpm); maternal IONV, Apgar scoring, UV blood gas |
| Kee 2015, Hong Kong [9] | 101 Healthy women | Spinal anesthesia with bupivacaine 11 mg + fentanyl 15 μg, rapid cohydration with Hartmann' solution 2 L, left tilt supine position, suprasternal Doppler (USCOM) for CO monitor | Closed-loop feedback computer-controlled infusion | NE 0–5 μg/min *vs* PE 0–100 μg/min for SBP near baseline with computer designed algorithm | Standardized CO, SV, SVR, HR, Apgar scoring, UA and UV blood gas, as well as UA and UV catecholamine, glucose, and lactate content |

CI = cardiac index, CO = cardiac output, DBP = diastolic blood pressure, HR = heart rate, IONV = intraoperative nausea and vomiting, LR = lactated ringers' solution, MDPE = median performance error, MDAPE = median absolute performance error, NE = norepinephrine, PE = phenylephrine, SBP = systolic blood pressure, SV = stroke volume, SVR = systemic vascular resistance, UA = umbilical artery, UV = umbilical vein, Wobble (the median value of the differences between each value of performance error and MDPE).

### 3.3. Risk of bias assessment and studies quality grading

Risk of bias was assessed using RevMan 5.3 (Fig. 2). Three reports were judged to have low-risk of bias and graded as high quality.[9,14,15] However, there were several disadvantages in the study by Vallejo et al[13] that were pointed by a following editorial.[16] First, the study adopted an open-label strategy, and group assignment was not blinded to the anesthesia provider, a serious disadvantage for a clinical trial. Second, the dose of 6 μg/min of phenylephrine in this study is prominently lower than the commonly used 25 to 100 μg/min and almost certainly less potent than 3 μg/min of norepinephrine when considering the potency ratio between phenylephrine and norepinephrine is nearly 13:1. Furthermore, there existed an observational bias, irrationality in group randomization, and inaccuracy in statistical analysis, collectively leading this study to a low quality.

### 3.4. Maternal outcomes

***3.4.1. Hypotension and hypertension.*** The definition of hypotension varied among trials (lower than 80%[9,14,15] or below baseline [13]), while the definition of hypertension was consistent in all four trials (higher than 120% of baseline) (Table 1). Results of the meta-analysis showed there was no difference between norepinephrine and phenylephrine groups for the management of hypotension (OR 0.64; 95% CI 0.37–1.10, $P = .11$) (Fig. 3A). Similarly, no difference was observed in the incidence of hypertension between groups (OR 0.74; 95% CI, 0.33–1.62, $P = .45$) (Fig. 3B).

***3.4.2. Bradycardia.*** Three trials collected data on maternal bradycardia, with varied definitions: HR < 50 bpm[15] or < 60 bpm.[13,14] When compared to bolus phenylephrine 100 μg to treat maternal hypotension, bolus norepinephrine 6 μg showed a 71% reduction in the incidence of bradycardia.[15] In another RCT trial, standardized HR in the first 20 minutes post spinal anesthesia was more frequently observed in the norepinephrine group than in the phenylephrine group ($P = .039$).[9] Meta-analysis results showed parturients who received norepinephrine were less likely to develop bradycardia (OR 0.29; 95% CI, 0.12–0.68, $P = .005$) (Fig. 3C).

***3.4.3. IONV.*** One trial observed an incidence of nausea, one observed vomiting.[13,15] However, another trial did not independently collect data on nausea or vomiting.[14] Considering the relatively small number of enrolled trials, we integrated data of nausea and vomiting to IONV, which revealed a significant decrease of IONV in the norepinephrine group when

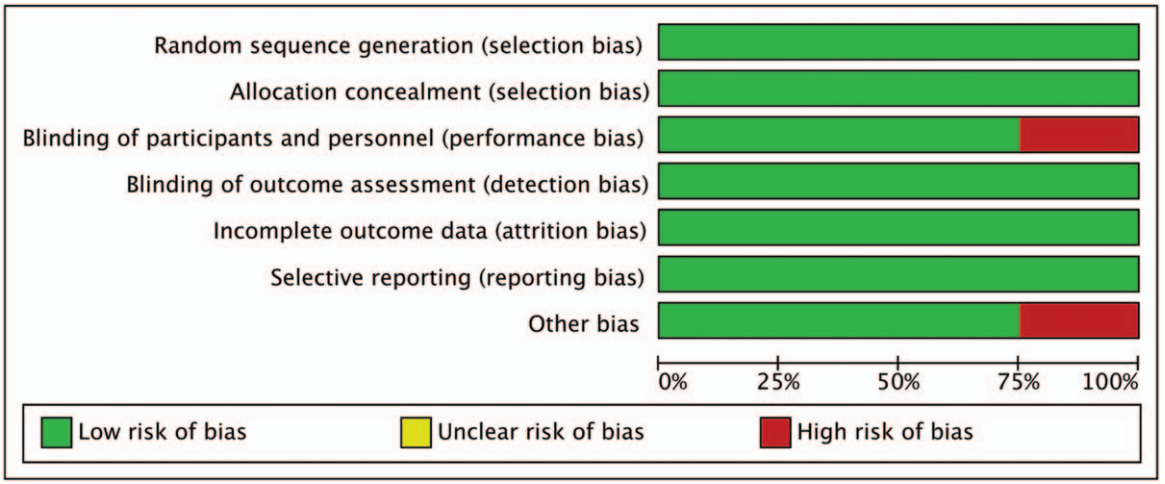


**Figure 2.** Risk of bias summary, presented as percentages across all included trials.

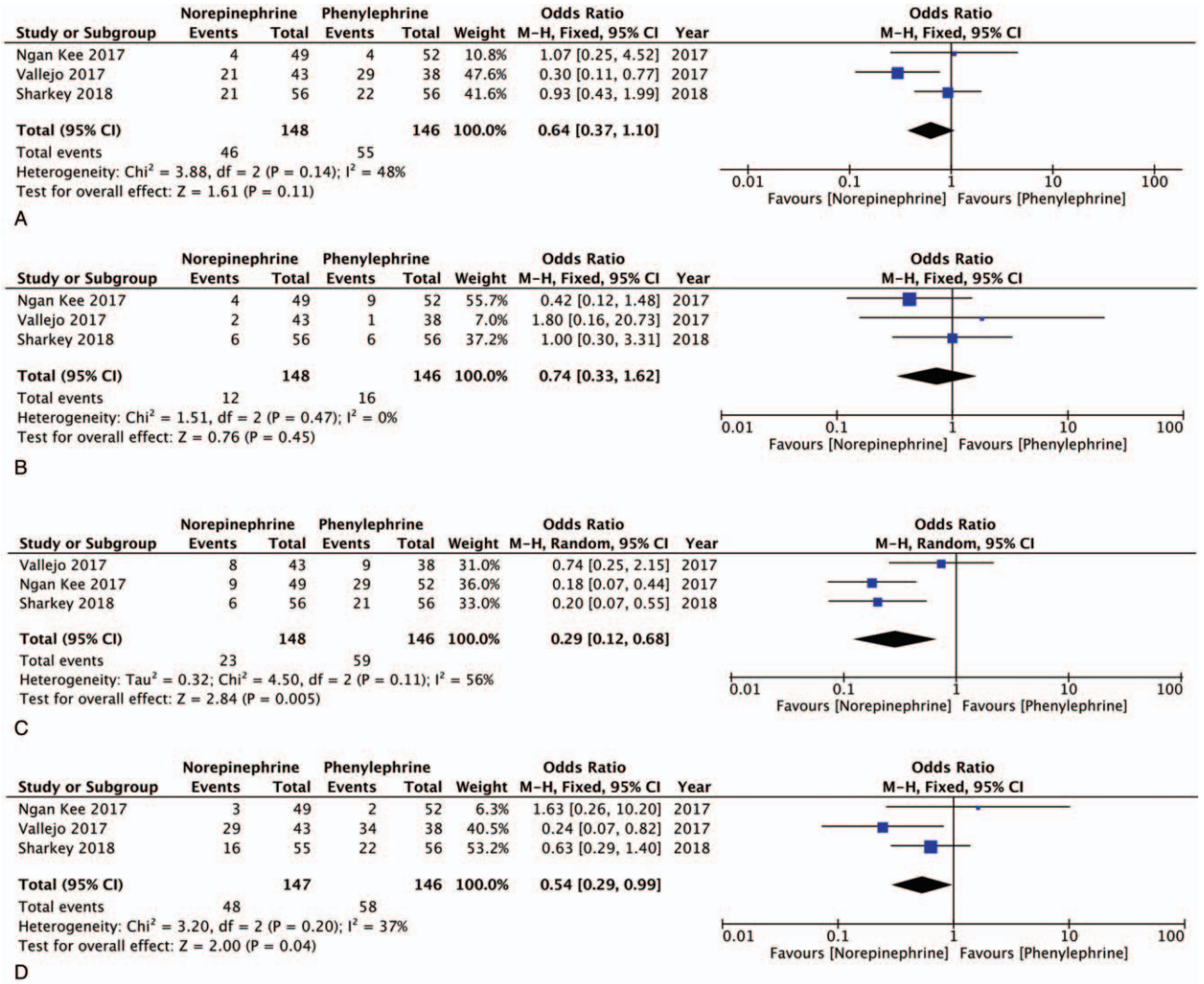


**Figure 3.** Forest plots and effect sizes of maternal outcomes across all included trials for incidence of hypotension (A), hypertension (B), bradycardia (C), and intraoperative nausea and vomiting (IONV) (D). IONV = intraoperative nausea and vomiting.

compared to the phenylephrine group (OR 0.54; 95% CI, 0.29–0.99, $P=.04$) (Fig. 3D).

***3.4.4. Maternal CO.*** Two trials examined maternal noninvasive CO post spinal anesthesia, but data was not pooled due to differences in data presentation. In the trial by Kee et al,[9] standardized maternal CO in the first 20 minutes postspinal anesthesia was higher and SVR was lower in the norepinephrine group than in the phenylephrine group ($P<.001$). In contrast, another trial showed no change in CO, CI, or SVR at time points including immediately before intrathecal injection, intrathecal injection, supine position with left uterine displacement, and at delivery.[13]

***3.4.5. BP control precision.*** Of the enrolled RCTs, only one trial compared BP control precision using performance error calculation, which included median performance error (MDPE, the median values of performance error for every patient), median absolute performance error (MDAPE, the median absolute values of performance error for every patient), Wobble (the median value of the differences between each value of performance error and MDPE), and divergence (a measure of BP control precision over time). Results showed that norepinephrine infusion was associated with a more precise control of BP (demonstrated by decreased MDPE, MDAPE, and Wobble) than phenylephrine infusion.[9]

### *3.5. Neonatal outcomes*

***3.5.1. Apgar scoring.*** The method of presenting Apgar scores differed among trials, including median (interquartile range),[15] percentage of values $<7$,[13] or percentage of values $<8$ at 1 min and 5 min.[9] For meta-analysis, we uniformly extracted data from these trials with Apgar scores $<7$ at 1 and 5 minutes. Results showed there was no significant difference in the risk of low Apgar score ($<7$) between norepinephrine and phenylephrine groups at 1 minute (risk difference [RD] −0.01, 95% CI −0.05 to 0.04, $P=.83$) (Fig. 4A) or at 5 minutes (RD −0.0, 95% CI −0.03 to 0.03, $P=.78$) (Fig. 4B).

***3.5.2. Umbilical cord blood gas.*** Sharkey et al[15] examined UA and UV blood gas, while Vallejo et al[13] examined only UV blood gas, including pH, $PO_2$, $PCO_2$, $HCO_3$, and base excess. All were observed within a normal range, without intergroup differences. A meta-analysis for UV blood gas showed there were no differences between groups with regard to pH (WMD −0.00, 95% CI −0.02 to 0.02, $P=.90$) (Fig. 4C), $PO_2$ (WMD 0.46, 95% CI −1.02 to 1.94, $P=.54$) (Fig. 4D), $PCO_2$ (WMD 0.24, 95% CI −1.24 to 1.71, $P=.75$) (Fig. 4E), or base excess (WMD -0.10, 95% CI −0.52 to 0.32, $P=.63$) (Fig. 4F).

### *3.6. Heterogeneity analysis and publication bias*

No obvious heterogeneity was observed among trials when evaluating the incidence of hypotension, hypertension, IONV, Apgar scoring, or UV blood gas (pH, $PO_2$, $PCO_2$, and base excess); $I^2$ was $<50\%$ in these cases. $I^2$ was 56% for the incidence of bradycardia. However, with a $Q$ test with $P>0.10$, we did not proceed to explore the possibility of slight heterogeneity. Further, Stata 15.1 software was applied to examine publication bias with Begg's funnel plots produced for each outcome; all $P$ values were higher than 0.05, indicating no obvious publication bias. Figure 5 shows Begg's funnel plots for the incidences of hypotension, hypertension, bradycardia, and IONV.

## 4. Discussion

In this systematic review and meta-analysis, results showed norepinephrine and phenylephrine had similar efficacies for managing maternal hypotension with diverse dosing regimens and administration paradigms that have been studied. Of note, women who received norepinephrine were less likely to experience bradycardia and IONV. Further, there was no significant difference between the two vasopressors in the incidence of neonatal Apgar scores $<7$ at 1 and 5 minutes or in UV blood gas. However, we did not find sufficient evidence with regard to the greater maternal CO and better BP control precision with the use of norepinephrine.

Maternal hypotension is a common phenomenon in parturients undergoing cesarean delivery with spinal anesthesia, with a decrease of SVR recognized as a significant contributor.[17] Accordingly, the pure α-agonist phenylephrine is the current gold standard and widely used in obstetric anesthesia. In contrast, use of norepinephrine to treat maternal hypotension is a recent advancement. As the literature is still limited, only 3 RCTs were enrolled in our meta-analysis.

Results showed similar efficacies of norepinephrine and phenylephrine for the prevention or treatment of maternal hypotension without an increase the incidence of unintended hypertension. In a previous dose-response study, sequential bolus norepinephrine and phenylephrine were applied to treat the first episode of hypotension. The authors obtained an ED90 of 18 μg for norepinephrine and an ED90 of 239 μg for phenylephrine, reaching a potency ratio approximately 13:1.[7] Almost at the same time, another dose-finding study suggested an ED90 of approximately 6 μg for norepinephrine to prevent maternal hypotension; the majority of those receiving a dose lower than 6 μg still presented with hypotension (5 in 6 cases).[8]

In our systematic review, enrolled trials used a closed-loop feedback computer-controlled infusion of norepinephrine 0 to 5 μg/min or a fixed rate infusion with 0.05 μg/kg/min (the equivalent of 3 μg/min for a parturient weighing 60 kg) to prevent maternal hypotension, or bolus 6 μg to treat it; all showed a definite efficacy. Further, in the trial by Kee et al,[14] computer-controlled norepinephrine infusion was associated with a more precise BP control, demonstrated by decreased MDPE, MDAPE, and Wobble when compared to phenylephrine. This plausible superiority of norepinephrine is attributed to its pharmacological properties such as a fast onset and short duration[18] that make accurate titration possible. However, due to the concern that computer-assisted infusion technology is currently not recommended for clinical practice,[19] Kee et al thereafter explored the efficacy of a simpler algorithm. They manually controlled the variable rate infusion of norepinephrine 0–5 μg/min to maintain BP near baseline and compared this with rescue bolus 5 μg whenever hypotension occurred.[20] They found the manually controlled infusion regimen was associated with a lower incidence of hypotension, a similar CO, and a better BP control precision than the rescue bolus. Although a relatively larger dose of norepinephrine is used with continuous infusion, no maternal or neonatal adverse outcomes were observed. These results suggest norepinephrine is effective for the management of parturients' BP. However, as only two trials observed maternal CO with different presentations and only one trial explored BP control precision, meta-analyses were not performed for CO or BP control precision.

Of note, this meta-analysis showed the incidence rate of maternal bradycardia was significantly lower with norepinephrine

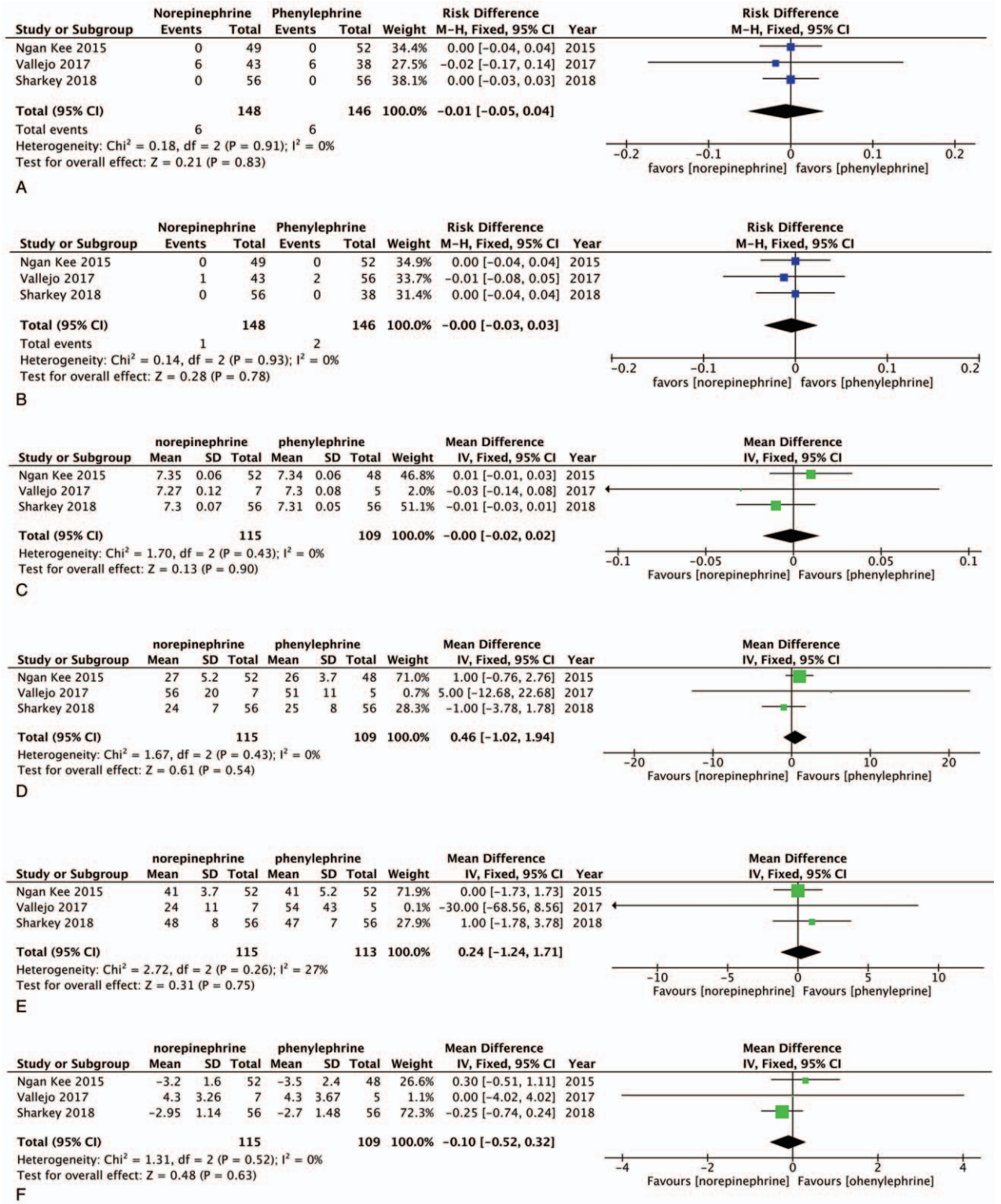


**Figure 4.** Forest plots and effect sizes of neonatal outcomes, including incidence of Apgar < 7 at 1 minute (A) and 5 minutes (B), as well as UV pH (C), $PO_2$ (D), $PCO_2$ (E), and base excess (F).

than with phenylephrine. The incidence of maternal bradycardia associated with phenylephrine was 55.8% in one trial. The incidence decreased by nearly two thirds in the norepinephrine treatment group (18.4%).[14] Maternal bradycardia may be due to a reflexive β-receptor mediated decrease in HR, or it may result from cardiac sympathetic denervation if the sensory block level is high. Either mechanism would be counteracted by β-receptor agonist activity. Therefore, as expected, norepinephrine demonstrates better HR maintenance and lower incidence of bradycardia.

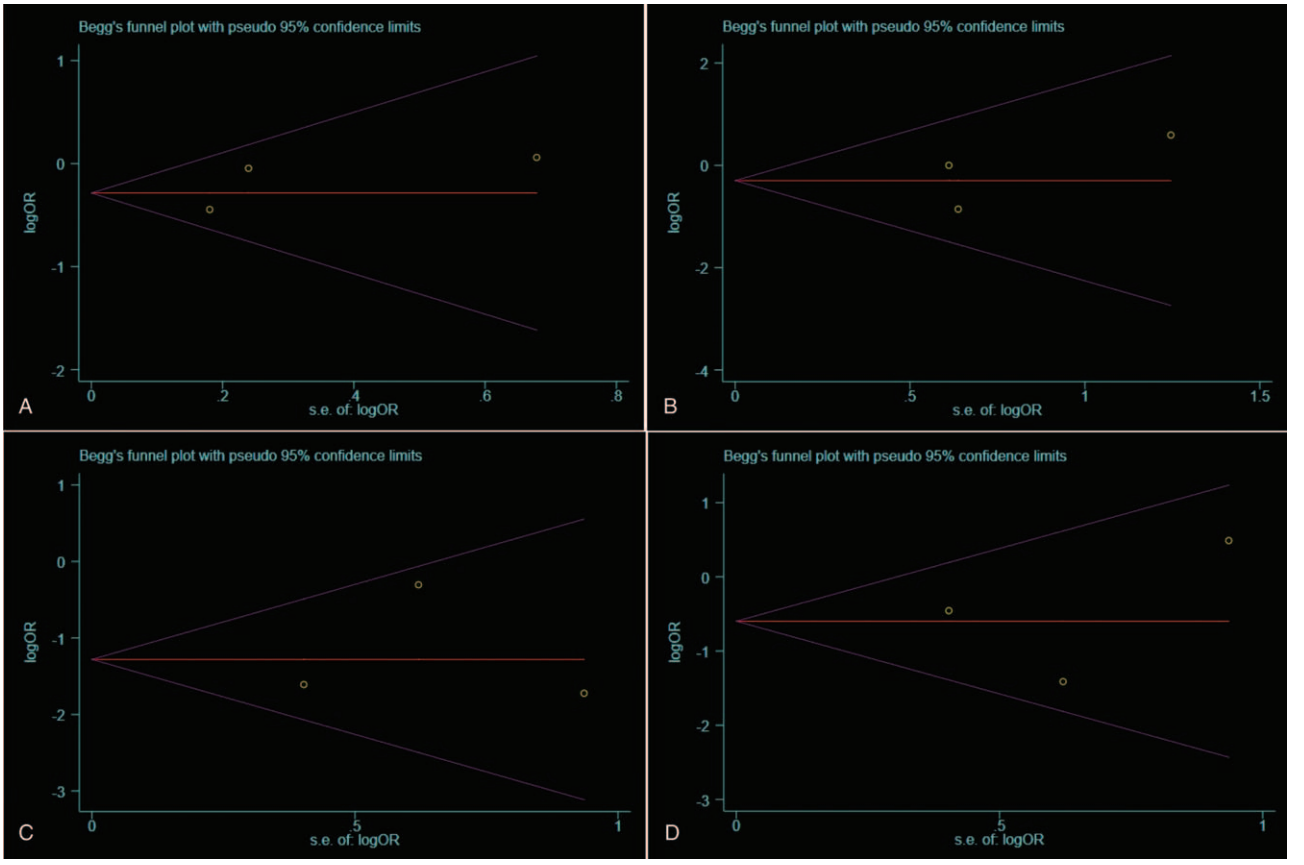


**Figure 5.** Begg's funnel-plot assessment of publication bias in trials that examined incidence of hypotension (A), hypertension (B), bradycardia (D), and intraoperative nausea and vomiting (IONV) (D). IONV = intraoperative nausea and vomiting.

It is also worth noting that parturients in the norepinephrine group experienced fewer incidents of IONV. Contributing factors of IONV in the context of cesarean delivery may include intrathecal opioid, hypotension, or uterine exteriorization. Although all the enrolled RCTs collected data until delivery, excluding the influence of uterine exteriorization, the sample sizes of the RCTs were not large enough to ascertain the exact contributor of IONV. Vallejo et al[13] observed a high incidence of IONV in the phenylephrine group (34 of 38 cases), and a decreased incidence in the norepinephrine group (29 of 43 cases). The authors suggested the high proportion in both groups might partially be attributed to the use of intrathecal morphine and fentanyl. A low propensity of norepinephrine to induce IONV may reflect a better gut and cerebral perfusion, followed by less serotonin release and less stimulation for the brainstem vomiting center; this is a favorable advantage when compared to phenylephrine.

Neonatal outcomes, including Apgar scoring and umbilical cord blood gas, were analyzed with meta-analysis. Although one trial observed a higher pH (7.35[7.34–7.37] vs 7.34[7.32–7.36] $P = .031$), $PO_2$ (12.7[11.3–14.4] vs 11.89[9.6–13.7] mm Hg, $P = .047$), and glucose (56[51–62] vs 51[44–56] mL/dL, $P < .001$) in UV blood gas in the norepinephrine group,[9] no intergroup difference between groups was found, with all values falling into a normal range. Another trial also showed that norepinephrine infusion may induce a dose-dependent increase in maternal and neonatal glucose.[6] The authors suggested this might result from a catecholamine-stimulated glucose-metabolism increase and a β-receptor mediated insulin-level decrease.[6,9] Further, norepinephrine is thought not to readily cross the placenta, which has the ability to break down catecholamines. In fact, as suggested by Kee et al, the use of norepinephrine may actually reduce fetal catecholamine levels compared to phenylephrine.[9] The greater neonatal pH, $PO_2$, and glucose content, together with lower umbilical plasma catecholamine concentrations, suggest a lower level of fetal stress with norepinephrine use than with phenylephrine use.[9]

A concern for norepinephrine application is vasoconstriction and skin necrosis, as the peripheral vein is commonly used in non-intensive care settings.[16] A recent study observed skin color in patients infused with normal saline or 5, 10, and 15 μg/kg/h norepinephrine; it showed the incidence of pale skin was similar among groups (3.3% vs 3.4% vs 20% vs 10.7%, respectively $P = .089$).[6] Other studies have also suggested the safety of norepinephrine for local tissue perfusion with an explanation as follows:[7,8,20] norepinephrine is diluted before use and administered in a running fluid for a relative short duration. Further, an equal potency of norepinephrine infusion or bolus has a theoretically similar vasoconstrictive potency as phenylephrine. Thus, the risk should be no different than that posed by phenylephrine. Furthermore, a previous study showed spinal anesthesia would increase skin perfusion, and this effect was not counteracted by norepinephrine application.[21] Instructions for commercially available norepinephrine (Levophed) do not emphasize that it needs to be given centrally rather than via a large vein, preferably antecubital, or that lower extremities should be avoided.[22]

There were several limitations to our meta-analysis. Only 3 trials with 294 parturients were included, with obvious differ-

ences in study design such as drug administration methods, the sample size calculation criteria, primary observational outcomes and their definitions, and hemodynamic management objectives. Further, in studies by Sharkey et al[15] and Vallejo et al,[13] additional bolus dosed of phenylephrine or ephedrine were used. The norepinephrine group may have received phenylephrine, which makes the comparison with the phenylephrine group less relevant, particularly regarding bradycardia. Additional ephedrine could interfere in the comparison between norepinephrine and phenylephrine efficacy and safety. Furthermore, the low quality of the study by Vallejo et al[13] inevitably reduced our confidence in the results of our meta-analysis.

Therefore, larger, well-designed RCTs are needed to compare the hypotension incidence in norepinephrine and phenylephrine groups. In addition, the efficacy and safety of norepinephrine need to be ascertained in high risk parturients with comorbid conditions such as cardiac disease, preeclampsia, or fetal distress. Importantly, certain details of norepinephrine application need to be examined, including the target blood pressure, intervention timing, as well as the dosing regimen and administration paradigm.

## 5. Conclusion

In summary, this systematic review and meta-analysis shows norepinephrine may be a promising alternative for phenylephrine for the management of maternal hypotension during cesarean delivery with spinal anesthesia in healthy, nonlaboring parturients. However, before routine clinical application, more well-designed RCTs are warranted to validate its efficacy and safety including in high risk parturients.

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