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SYSTEMATIC REVIEW

Norepinephrine versus phenylephrine for managing maternal hypotension during cesarean delivery under spinal anesthesia: a meta-analysis of maternal and neonatal outcomes

Jianli Song[1], Xi Xu[2], Qiang Li[1], Bin Lu[1], Xuan Yu[1], Guo Mu[1,*]

[1]Department of Anesthesiology, Zigong Fourth People's Hospital, 643000 Zigong, Sichuan, China
[2]Department of Anesthesiology, The Fushun People's Hospital, 643000 Zigong, Sichuan, China

***Correspondence**
muguo@zg120.cn
(Guo Mu)

Abstract

Norepinephrine or phenylephrine administration to prevent and treat hypotension during spinal anesthesia for cesarean section has been a significant topic of discussion. This meta-analysis aimed to update existing evidence and provide further insights into neonatal and maternal outcomes associated with norepinephrine and phenylephrine. Review of randomized controlled trials (RCTs) was performed to assess the effectiveness of norepinephrine and phenylephrine in managing maternal hypotension during cesarean delivery under spinal anesthesia. Neonatal umbilical cord blood pH and maternal hypotension were the primary outcomes. Based on the analysis of 26 RCTs with 2984 participants, we found no significant difference between the norepinephrine and phenylephrine groups in umbilical artery pH in neonates (mean difference (MD) 0.00; 95% confidence interval (CI) −0.00 to 0.01, $p = 0.20$). Neonates Apgar scores did not differ between both groups. Norepinephrine was associated with lower incidences of bradycardia (risk ratio (RR) 0.44; 95% CI 0.37 to 0.51, $p < 0.001$) and reactive hypertension (RR 0.53; 95% CI 0.39 to 0.72, $p < 0.001$) in parturient women than phenylephrine. In neither group did umbilical cord blood levels of partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$) and base excess (BE) levels of neonates differ significantly, nor did maternal hypotension, nausea or vomiting incidence during delivery. For maternal hypotension after spinal anesthesia, norepinephrine and phenylephrine did not significantly differ in neonatal acidemia. Despite similarities to phenylephrine in managing hypotension and maintaining maternal hemodynamic stability, norepinephrine is a promising alternative.

Keywords

Norepinephrine; Phenylephrine; Maternal hypotension; Caesarean delivery; Spinal anesthesia

1. Introduction

Spinal anesthesia is considered the preferred technique for both elective and emergency cesarean sections due to its excellent operative conditions and high tolerance levels [1]. However, hypotension remains a common spinal anesthesia complication. Post-spinal hypotension incidence can reach 70–80% without prophylactic vasoactive drugs [2]. Maternal symptoms of severe hypotension include nausea, vomiting and dyspnea. Hypotension severity and duration are associated with adverse effects on newborns, such as reduced Apgar scores and acidosis [3]. Therefore, maternal hypotension should be prevented efficiently.

A recent standard of care recommends prophylactic use of vasopressors and fluid boluses [4–6]. Phenylephrine, a potent alpha-adrenergic receptor agonist, has emerged as a primary vasopressor in obstetrics [5, 7]. Baroreceptor-mediated bradycardia and maternal cardiac output reductions are possible side effects [8, 9]. There is no evidence that these changes have adverse effects on neonates at the moment. Nevertheless, researchers have raised concerns regarding the lack of appropriate assessment techniques and longer follow-ups [10]. Norepinephrine, a strong alpha-adrenergic receptor agonist with beta-adrenergic effects, has been found to be equivalent to phenylephrine in maintaining blood pressure while increasing heart rate (HR) and cardiac output (CO) [8, 11]. Based on systematic evaluations, norepinephrine offers better hemodynamic stability and fewer side effects in controlling maternal hypotension than phenylephrine [12]. However, these evaluations were based on small-sample studies that rarely examined norepinephrine's impact on fetal acid-base status. A single Bayesian network meta-analysis indicated that

norepinephrine adversely affected fetal acid-base status less frequently [13]. Moreover, the effectiveness of norepinephrine and phenylephrine in managing maternal hypotension during cesarean sections was recently evaluated in randomized controlled trials using neonatal outcomes as the primary research indicator [14–16].

This study conducted a systematic review and meta-analysis to update existing evidence and better understand norepinephrine's effects on neonatal and maternal outcomes. We aimed to develop updated evidence-based guidelines for anesthesiologists to treat and prevent maternal hypotension during cesarean sections under spinal anesthesia on the selection of norepinephrine and phenylephrine.

2. Methods

This study adhered to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [17]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under Registration ID CRD42022361087.

2.1 Outcomes

We evaluated neonatal and maternal outcomes separately. In neonatal assessment, umbilical cord blood pH (including that of the umbilical artery and vein) was the primary indicator. Umbilical cord PaO_2, $PaCO_2$ and base excess (BE), umbilical artery lactate, and APGAR scores of neonates at 1 minute and 5 minutes were secondary outcomes. A prespecified subgroup analysis was performed to determine whether prophylactic infusion or bolus therapy of norepinephrine or phenylephrine affected maternal and neonatal outcomes in treating maternal hypotension.

In maternal assessment, the incidence of hypotension was the primary outcome. Hypotension is defined as a reduction in blood pressure even when norepinephrine or phenylephrine is administered. In the enrolled studies, hypotension was commonly referred to as "<80% baseline systolic blood pressure (SBP)" or "<100 mmHg". The incidence of bradycardia, nausea, vomiting and reactive hypertension were secondary outcomes. The majority of studies defined bradycardia by HR <60 beats/min, with only six studies using HR <50 beats/min. In almost all included studies, reactive hypertension was defined as SBP >120% of the baseline value.

2.2 Selection and exclusion criteria

A meticulously search was conducted on PubMed, Web of Science and Cochrane Library, spanning their inception until 18 September 2022. **Supplementary Table 1** outlines the detailed search strategy. Clinical trial registries were explored to identify grey literature. A comprehensive review of all included studies' reference lists was conducted to ensure no studies had been overlooked in the initial electronic search. Language, sample size or publication date were not restricted. The inclusion criteria were: (1) population—parturient women undergoing spinal anesthesia elective cesarean delivery, (2) intervention—intraoperative norepinephrine intraoperatively to manage or prevent post-spinal hypotension, (3) control—phenylephrine intraoperatively to manage or prevent post-spinal hypotension, (4) outcomes—eligible studies reporting at least one predetermined outcome, and (5) study design—randomized controlled trials. Exclusion criteria included (1) general anesthesia cesarean deliveries, (2) failure to extract data, and (3) lack of full text access.

2.3 Data extraction

Potential inclusions were independently screened by Jianli Song and Xi Xu. All potentially eligible studies were reviewed in detail, and data was extracted using an Excel spreadsheet extraction table. Basic information, treatment methods and outcome indicators were meticulously collected from articles that met the criteria. The two reviewers resolved any disagreements through discussion or mediation by Guo Mu.

2.4 Risk of bias assessment

Using the Cochrane Collaboration risk-of-bias tool, two reviewers independently assessed the bias risk of the included studies. Study bias was classified as high, low or unclear. For consistency, each study underwent cross-checking, and discrepancies were resolved by involving a third reviewer as a mediator or a discussion between the two reviewers.

2.5 Statistical analysis

In each study, continuous and dichotomous data were extracted. Continuous data were presented as mean difference (MD) with a 95% confidence interval (CI). Dichotomous data were presented as a risk ratio (RR) with a 95% CI. Using Wan *et al.*'s [18] method, studies with median and range or interquartile range were converted to mean and standard deviation [18]. Statistical heterogeneity was evaluated using I^2 statistics. A fixed-effects model was applied, and a random-effects model was adopted in cases of significant heterogeneity (p-value of chi-square test < 0.10 and $I^2 > 50\%$). To investigate heterogeneity sources, subgroup and sensitivity analyses were performed when heterogeneity was high. One study at a time was omitted during the sensitivity analysis to determine its impact on the overall pooled estimate. Considering clinical and methodological diversity among studies, a random-effects model was used to analyze the effect sizes of primary and secondary outcomes. Over 10 studies were evaluated for potential publication bias using funnel plot symmetry. We pre-planned a subgroup analysis based on drug administration protocol (prophylactic infusion versus bolus treatment for maternal hypotension) in anticipation of heterogeneity across trials. Statistical studies and meta-analyses were conducted with Review Manager (RevMan, V.5.4.1), with a two-sided statistical significance set at $p < 0.05$.

3. Results

3.1 Search outcomes and study characteristics

This meta-analysis included 26 RCTs. An initial electronic search yielded 894 citations, and a review of gray literature added 33 more. A thorough text review of 54 studies was

identified as potentially eligible. After eliminating duplicates and disqualified studies, this meta-analysis included 26 RCTs with 2984 participants [8, 14–16, 19–40] (Fig. 1A). This analysis includes studies from 2015 to 2022, with sample sizes ranging from 44 to 668 patients. Among the considered studies, 14 trials used norepinephrine or phenylephrine as a prophylactic infusion to prevent maternal hypotension [8, 15, 16, 19–29], 9 used bolus administration for treatment [14, 30–37], 2 used bolus administration for prevention or treatment [38, 39], and 1 used an infusion or bolus for either prophylactic or therapeutic purposes [40]. Using a literature-by-exclusion approach, sensitivity analyses were conducted on outcomes exhibiting high heterogeneity. Fig. 1B,C summarizes the risk of bias for individual studies and the overall risk of bias. Table 1 summarizes the key features of the included studies.

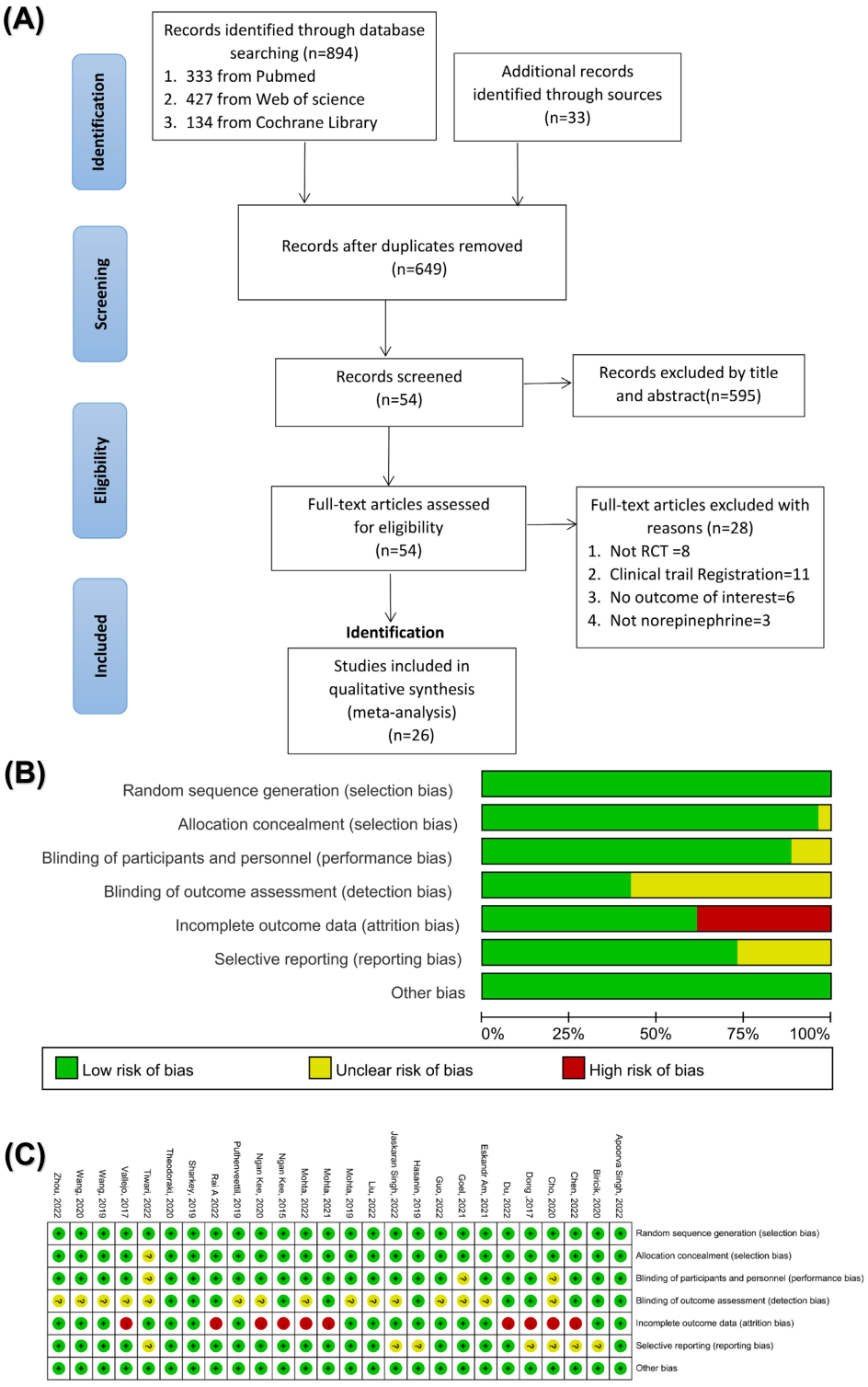

FIGURE 1. Literature inclusion process and quality evaluation. (A) PRISMA flow diagram of study selection. (B) Risk of bias summary of the included studies. (C) Risk of bias graph of the included studies. RCT: randomized controlled trial.

TABLE 1. Main characteristics of included studies.

Trail	Country	Type of surgery	Total patients	Mode of administration	Norepinephrine group	Phenylephrine group	Primary outcome	Inclusion indicators
Ngan Kee, 2015	China	Elective CD under spinal anesthesia	101	Prophylactic infusions	Infusion rate was within the limits of 0 to 60 mL/h (5 μg/mL, n = 49)	Infusion rate was within the limits of 0 to 60 mL/h (100 μg/mL, n = 52)	CO	①②④⑤⑥⑦
Vallejo, 2017	USA	Elective CD under spinal anesthesia	81	Prophylactic infusions	Fixed-rate infusions at 0.05 μg/kg/min (n = 43)	Fixed-rate infusions at 0.1 μg/kg/min (n = 38)	The number and total dose of rescue bolus interventions	②⑤⑥
Dong, 2017	China	Elective CD under spinal anesthesia	126	Prophylactic infusions	50 μg was given a bolus prophylactically (10 μg/mL, n = 62)	50 μg was given a bolus prophylactically (50 μg/mL, n = 64)	Maternal hypotension	①②⑤⑥⑦
Hasanin, 2019	Egypt	Elective CD under spinal anesthesia	123	Prophylactic infusions	Infusion with a starting rate of 0.05 μg/kg/min (4 μg/mL, n = 60)	Infusion with a starting rate of 0.75 μg/kg/min (50 μg/mL, n = 63)	Post-spinal hypotension	①③④⑤⑥⑦
Mohta, 2019	India	Elective CD under spinal anesthesia	90	Bolus for treatment	5 μg was given a bolus for treatment (5 μg/mL, n = 45)	100 μg was given a bolus for treatment (100 μg/mL, n = 45)	Maternal bradycardia	①②③⑤⑦
Puthenveettil, 2019	India	Elective CD under spinal anesthesia	50	Bolus for treatment	4 μg was given a bolus for treatment (4 μg/mL, n = 25)	50 μg was given a bolus for treatment (50 μg/mL, n = 25)	The number of bolus doses of interventions	②③⑤⑥
Sharkey, 2019	Canada	Elective CD under spinal anesthesia	112	Bolus for treatment	6 μg was given a bolus for treatment (6 μg/mL, n = 56)	100 μg was given a bolus for treatment (100 μg/mL, n = 56)	Maternal bradycardia	①②③④⑤⑥⑦
Wang, 2019	China	Elective CD under spinal anesthesia in patients with pre-eclampsia	111	Bolus for treatment	4 μg was given a bolus for treatment (4 μg/mL, n = 56)	50 μg was given a bolus for treatment (50 μg/mL, n = 55)	The overall SBP and HR	①④⑤⑥
Biricik, 2020	Turkey	Elective CD under spinal anesthesia	80	Prophylactic infusion	Infusion at a fixed rate of 30 mL/h (5 μg/mL, n = 40)	Infusion at a fixed rate of 30 mL/h (100 μg/mL, n = 40)	Maternal hypotension	②④⑤⑥
Theodoraki, 2020	Greece	Elective CD under spinal anesthesia	82	Prophylactic infusion	Infusion at a fixed rate of 30 mL/h (5 μg/mL, n = 41)	Infusion at a fixed rate of 30 mL/h (100 μg/mL, n = 41)	Maternal bradycardia	②③④⑤⑥

TABLE 1. Continued.

Trail	Country	Type of surgery	Total patients	Mode of administration	Norepinephrine group	Phenylephrine group	Primary outcome	Inclusion indicators
Ngan Kee, 2020	China	Elective and non-elective CD under spinal anesthesia	668	prophylactically or therapeutically	Infusion or bolus (6 μg/mL, n = 333)	Infusion or bolus (100 μg/mL, n = 335)	UA pH	①②④⑤⑥
Cho, 2020	Korea	Elective CD under spinal anesthesia	44	Bolus for treatment	5 μg was given a bolus for treatment (5 μg/mL, n = 22)	100 μg was given a bolus for treatment (100 μg/mL, n = 22)	CO	①⑤⑥
Wang, 2020	China	Elective CD under spinal anesthesia	102	Bolus for prevention and treatment	8 μg was given a bolus for prevention and treatment (8 μg/mL, n = 52)	100 μg was given a bolus for prevention and treatment (100 μg/mL, n = 50)	CO	①②③⑤⑥⑦
Eskandr Am, 2021	Egypt	Elective CD under spinal anesthesia	50	Prophylactic infusion	Infusion at a rate of 0.05 μg/kg/min (n = 25)	Infusions at a rate of 0.1 μg/kg/min (n = 25)	Post-spinal hypotension	①③⑤⑥
Goel, 2021	India	Elective CD under spinal anesthesia	200	Prophylactic infusion	Infusion rate was within the limits of 0 to 60 mL/h (NE: 5 μg/mL, n = 100)	Infusion rate was within the limits of 0 to 60 mL/h (PE: 100 μg/mL, n = 100)	Maternal hemodynamics	⑤⑥⑦
Mohta, 2021	India	Elective CD under spinal anesthesia in patients with pre-eclampsia	86	Bolus for treatment	4 μg was given a bolus for treatment (4 μg/mL, n = 43)	50 μg was given a bolus for treatment (50 μg/mL, n = 43)	UA pH	①②⑤
Apoorva Singh, 2022	India	Elective CD under spinal anesthesia	100	Prophylactic infusion	Infusion at a fixed-rate of 50 mL/h (6 μg/mL, n = 50)	Infusion at a fixed-rate of 50 mL/h (120 μg/mL, n = 50)	UA BE	①
Zhou, 2022	China	Elective CD under spinal anesthesia	50	Prophylactic infusion	Infusion at an initial rate of 30 mL/h (8 μg/mL, n = 25)	Infusion at an initial rate of 30 mL/h (100 μg/mL, n = 25)	UA pH	①②③④⑤⑥⑦
Tiwari, 2022	India	Elective CD under spinal anesthesia	126	Bolus for treatment	4 μg was given a bolus for treatment (4 μg/mL, n = 63)	50 μg was given a bolus for treatment (50 μg/mL, n = 63)	Post-spinal hypotension	②③⑤⑥
Jaskaran Singh, 2022	India	Elective CD under spinal anesthesia	60	Prophylactic infusion	Infusion at the rate of 60 mL/h (2.5 μg/mL, n = 30)	Infusion at the rate of 60 mL/h (50 μg/mL, n = 30)	UA pH	①②③④⑤⑥⑦

TABLE 1. Continued.

Trail	Country	Type of surgery	Total patients	Mode of administration	Norepinephrine group	Phenylephrine group	Primary outcome	Inclusion indicators
Guo, 2022	China	Elective CD under spinal anesthesia in patients with pre-eclampsia	138	Prophylactic infusion	Fixed-rate infusions at 0.05 μg/kg/min (n = 69)	Fixed-rate infusions at 0.625 μg/kg/min (n = 69)	Maternal bradycardia and hypotension	①③④⑤⑥⑦
Mohta, 2022	India	Emergency CD under spinal anesthesia in patients with fetal compromise	100	Bolus for treatment	8 μg was given a bolus for treatment (8 μg/mL, n = 50)	100 μg was given a bolus for treatment (100 μg/mL, n = 50)	UA pH	①②③⑤
Du, 2022	China	Elective CD under spinal anesthesia in healthy twin pregnancies	62	Prophylactic infusion	Infusion at an initial rate of 60 mL/h (6 μg/h, n = 31)	Infusion at an initial rate of 60 mL/h (100 μg/h, n = 31)	CO	②③④⑤⑥⑦
Chen, 2022	China	Elective CD under spinal anesthesia in healthy twin pregnancies	100	Prophylactic infusion	Infusion at an initial rate of 24 mL/h (8 μg/h, n = 50)	Infusion at an initial rate of 24 mL/h (100 μg/h, n = 50)	The change in HR and BP	①②③④⑤⑥⑦
Liu, 2022	China	Elective CD under spinal anesthesia	52	Prophylactic infusion	Infusion at an initial rate of 0.3 μg/kg/h (16 μg/h, n = 26)	Infusion at an initial rate of 0.3 μg/kg/h (108 μg/h, n = 26)	UA pH	①②④⑤⑥
Rai. A, 2022	India	Elective CD under spinal anesthesia	90	Bolus for treatment	1 mL was given boluses for treatment (100 μg/mL, n = 45)	1 mL was given boluses for treatment (7.5 μg/mL, n = 45)	UA pH	①②⑤⑦

CD: cesarean delivery; UA: umbilical artery; CO: cardiac output; SBP: systolic blood pressure; HR: heart rate; BP: blood pressure; BE: base excess. ① *UA blood gas analysis,* ② *Umbilical venous (UV) blood gas analysis,* ③ *Apgar scores in 1-min and 5-min,* ④ *Hypotension,* ⑤ *Bradycardia,* ⑥ *Nausea or vomiting,* ⑦ *Reactive hypertension.*

3.2 Primary outcomes of neonates: the pH of umbilical cord blood

3.2.1 Umbilical artery pH

19 studies comprising 2293 neonates reported umbilical artery pH [8, 14–16, 20, 23, 25–27, 29, 30, 32–35, 37–39]. In meta-analysis, norepinephrine did not significantly differ from phenylephrine in neonates' umbilical artery pH during cesarean section under spinal anesthesia to prevent and treat maternal hypotension. The MD (95% CI) of 0.00 (−0.00 to 0.01; $p = 0.20$) was observed (Fig. 2A). Subgroup analysis revealed no significant effect related to drug administration method ($p = 0.63$, Fig. 2B). Funnel plot analysis showed no significant asymmetry, indicating a low likelihood of publication bias (**Supplementary Fig. 1A**).

3.2.2 Umbilical venous pH

19 studies involving 2139 neonates reported umbilical venous pH. According to the meta-analysis based on these studies, norepinephrine used during cesarean section under spinal anesthesia led to higher neonates' umbilical venous pH than phenylephrine. The MD (95% CI) was 0.01 (0.00 to 0.01; $p = 0.001$) (Fig. 3A). Subgroup analysis suggested that the drug administration mode had no effect on umbilical venous pH in neonates, with moderate heterogeneity ($p = 0.09$, $I^2 = 65\%$) (Fig. 3B). Funnel plot analysis visually indicated no significant asymmetry, indicating a low probability of publication bias (**Supplementary Fig. 1B**).

3.3 Secondary neonatal outcomes

3.3.1 Umbilical cord PaO_2

18 studies involving 2233 neonates reported umbilical artery PaO_2 and 18 studies involving 2010 neonates reported umbilical venous PaO_2. The meta-analysis of the relevant 18 studies found no significant differences in neonates' umbilical artery PaO_2, with a MD (95% CI) of 0.41 mmHg (−0.46 to 1.29; $p = 0.35$) (Fig. 4A). Based on the other set, the meta-analysis found no significant differences in umbilical venous PaO_2, with a MD (95% CI) of 0.73 mmHg (−0.50 to 1.96; $p = 0.24$) (Fig. 4B).

3.3.2 Umbilical cord $PaCO_2$

18 studies involving 2233 neonates reported umbilical artery $PaCO_2$ and 18 studies involving 2148 neonates reported umbilical venous $PaCO_2$. A meta-analysis of 18 studies showed no significant differences in neonates' umbilical artery $PaCO_2$, with a MD (95% CI) of 0.22 mmHg (−0.34 to 0.79; $p = 0.44$) (Fig. 5A). Based on the other set, the meta-analysis found no significant differences in umbilical venous $PaCO_2$, with a MD (95% CI) of −0.34 mmHg (−1.41 to 0.73; $p = 0.54$) (Fig. 5B).

3.3.3 Umbilical cord base excess (BE)

16 studies reported umbilical artery BE in 2060 neonates and 16 studies reported umbilical venous BE in 1972 neonates. A meta-analysis of 16 studies showed no statistical differences in neonates' umbilical artery BE, with a MD (95% CI) of 0.07 (−0.19 to 0.33; $p = 0.58$). Based on the other set, the meta-analysis found no significant differences in neonates' umbilical venous BE, with a MD (95% CI) of 0.24 (−0.15 to 0.64; $p = 0.22$) (**Supplementary Fig. 2**).

3.3.4 Umbilical artery lactate

11 studies reported umbilical artery lactate in 996 neonates. Based on these 11 studies, a meta-analysis showed no significant difference in umbilical artery lactate levels in neonates, with a MD (95% CI) of 0.04 mmol/L (−0.07 to 0.15; $p = 0.47$) (**Supplementary Fig. 3**).

3.3.5 Apgar scores of neonates

14 studies reported APGAR scores at 1 minute and 5 minutes, including 1239 neonates, and 6 reported APGAR scores <7 at 1 minute or 5 minutes, encompassing 1195 neonates. APGAR scores in neonates at 1 minute and 5 minutes were not significantly different based on a meta-analysis of 14 studies (**Supplementary Fig. 4A**). Moreover, no significant differences were observed in APGAR scores <7 at 1 minute and 5 minutes (**Supplementary Fig. 4B**).

3.4 Maternal primary outcomes: the incidence of hypotension after vasopressor-use

12 studies reported maternal hypotension involving 1828 parturient women. According to the meta-analysis, hypotension incidence was not significantly different between the 12 studies, with a RR (95% CI) of 1.12 (1.00 to 1.25; $p = 0.06$) (Fig. 6A). There was no subgroup effect related to drug administration mode ($p = 0.46$) (Fig. 6B). Funnel plot analysis suggested visually no significant asymmetry, indicating a low probability of publication bias (**Supplementary Fig. 5**).

3.5 Maternal secondary outcomes

3.5.1 The incidence of maternal bradycardia

25 studies involving 2878 parturient women reported maternal bradycardia. According to the meta-analysis, bradycardia incidence was not significantly different between the 25 studies, with a RR (95% CI) of 0.44 (0.37 to 0.51; $p < 0.001$) (Fig. 7). No subgroup effect related to drug administration mode was observed ($p = 0.84$). Also, there were no differences in either the prophylactic infusion group (RR 0.39, 95% CI 0.29 to 0.54, $p < 0.001$) or the bolus group (MD 0.41, 95% CI 0.29 to 0.58, $p < 0.001$) (**Supplementary Fig. 6**).

3.5.2 The incidence of maternal nausea or vomiting

21 studies encompassing 2514 parturient women, reported maternal nausea or vomiting. Based on these 21 studies, a meta-analysis showed no significant difference in nausea or vomiting incidence, with a RR (95% CI) of 1.00 (0.85 to 1.18; $p = 0.97$) (Fig. 8). There was no subgroup effect related to drug administration mode ($p = 0.41$). Neither the prophylactic infusion group (RR 0.99, 95% CI 0.71 to 1.37, $p = 0.94$) or the bolus group (RR 0.79, 95% CI 0.51 to 1.21, $p = 0.27$) showed a significant difference (**Supplementary Fig. 7**).

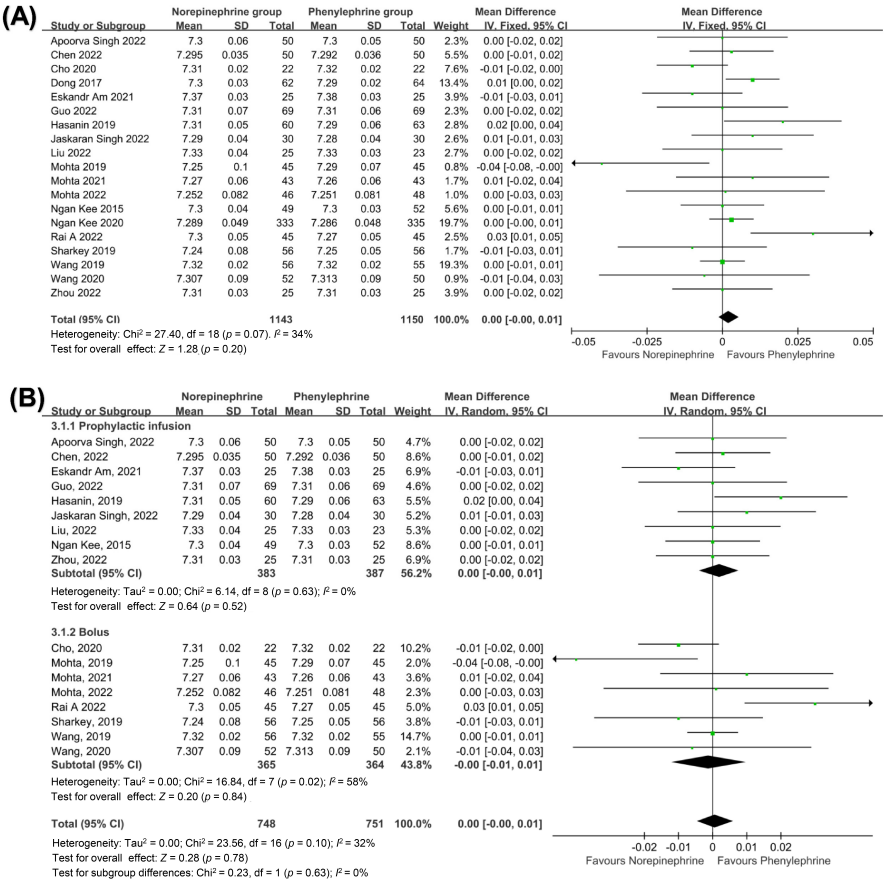

FIGURE 2. Umbilical artery pH. (A) Forest plot for umbilical artery pH. (B) Forest plot for subgroup analysis of umbilical artery pH. CI: confidence interval; SD: standard deviation.

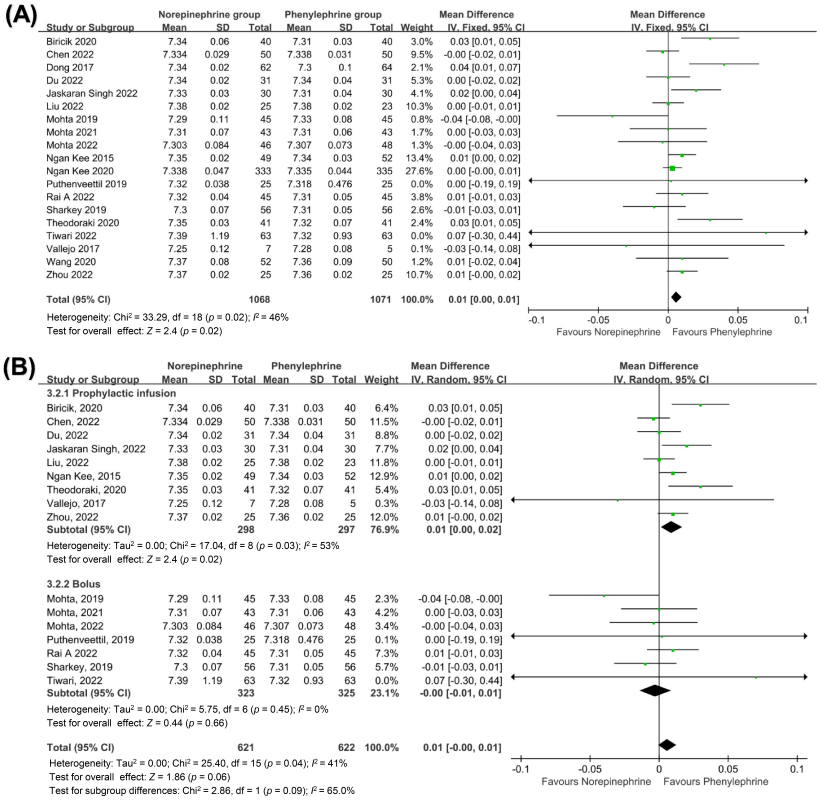

FIGURE 3. Umbilical venous pH. (A) Forest plot for umbilical venous pH. (B) Forest plot for subgroup analysis of umbilical venous pH. CI: confidence interval; SD: standard deviation.

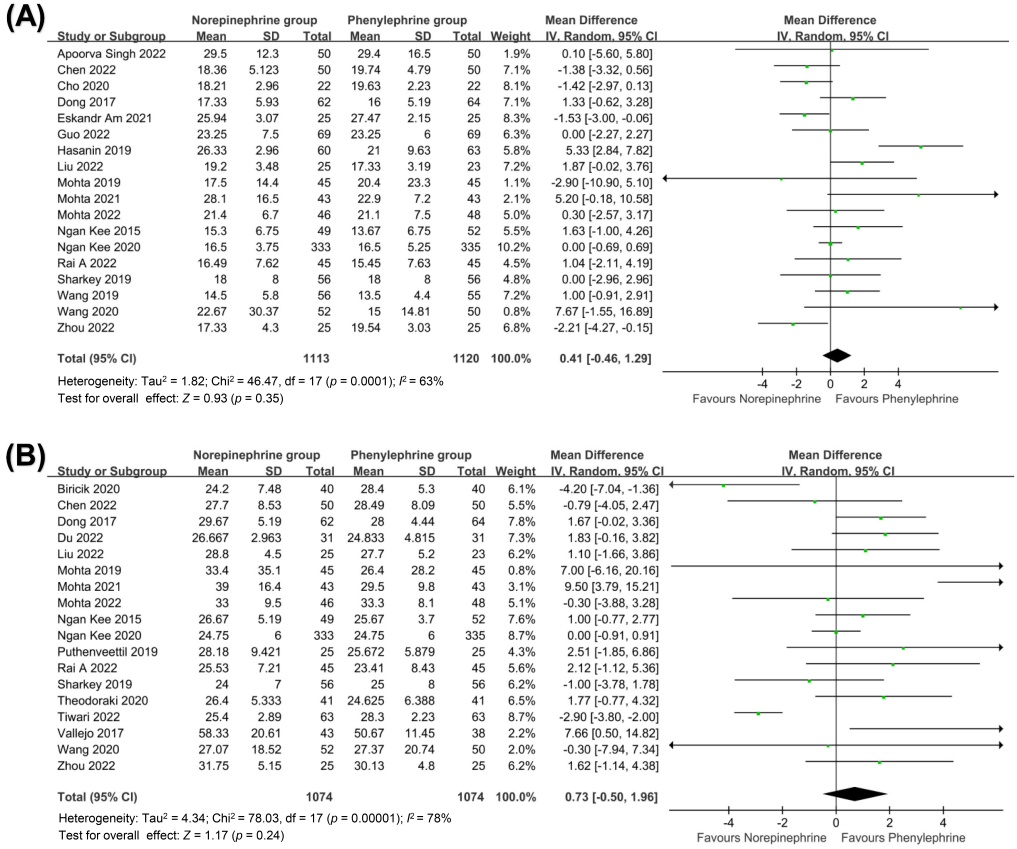

FIGURE 4. Umbilical cord PaO_2. (A) Forest plot for umbilical artery PaO_2. (B) Forest plot for umbilical venous PaO_2. CI: confidence interval; SD: standard deviation.

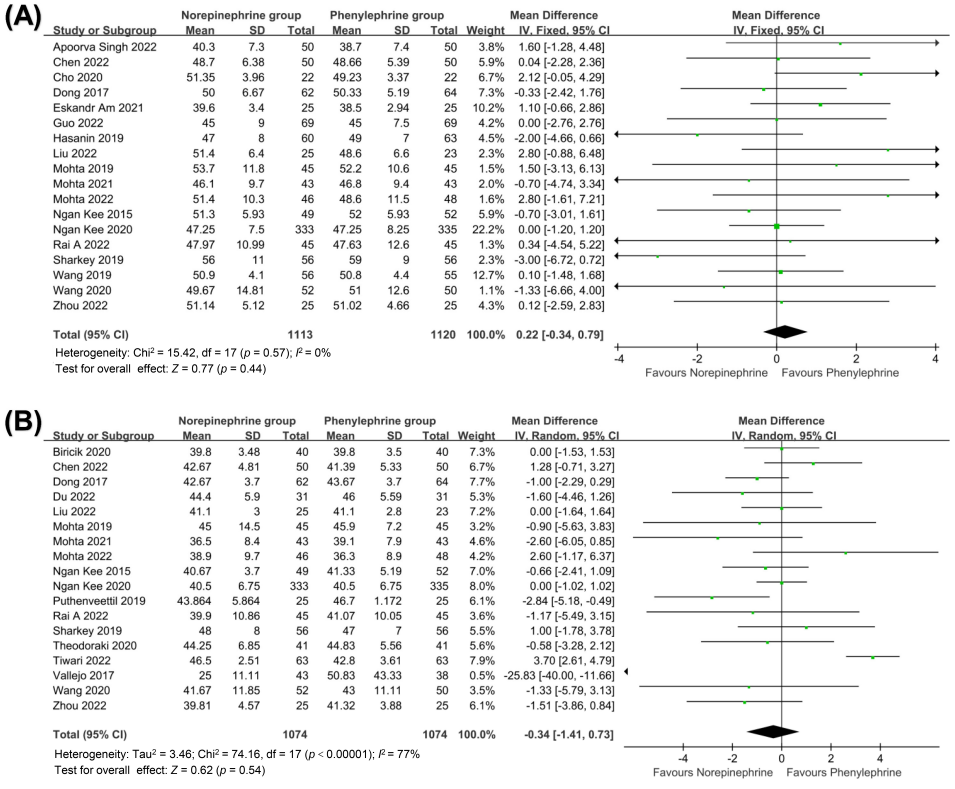

FIGURE 5. Umbilical cord $PaCO_2$. (A) Forest plot for umbilical artery $PaCO_2$. (B) Forest plot for umbilical venous $PaCO_2$. CI: confidence interval; SD: standard deviation.

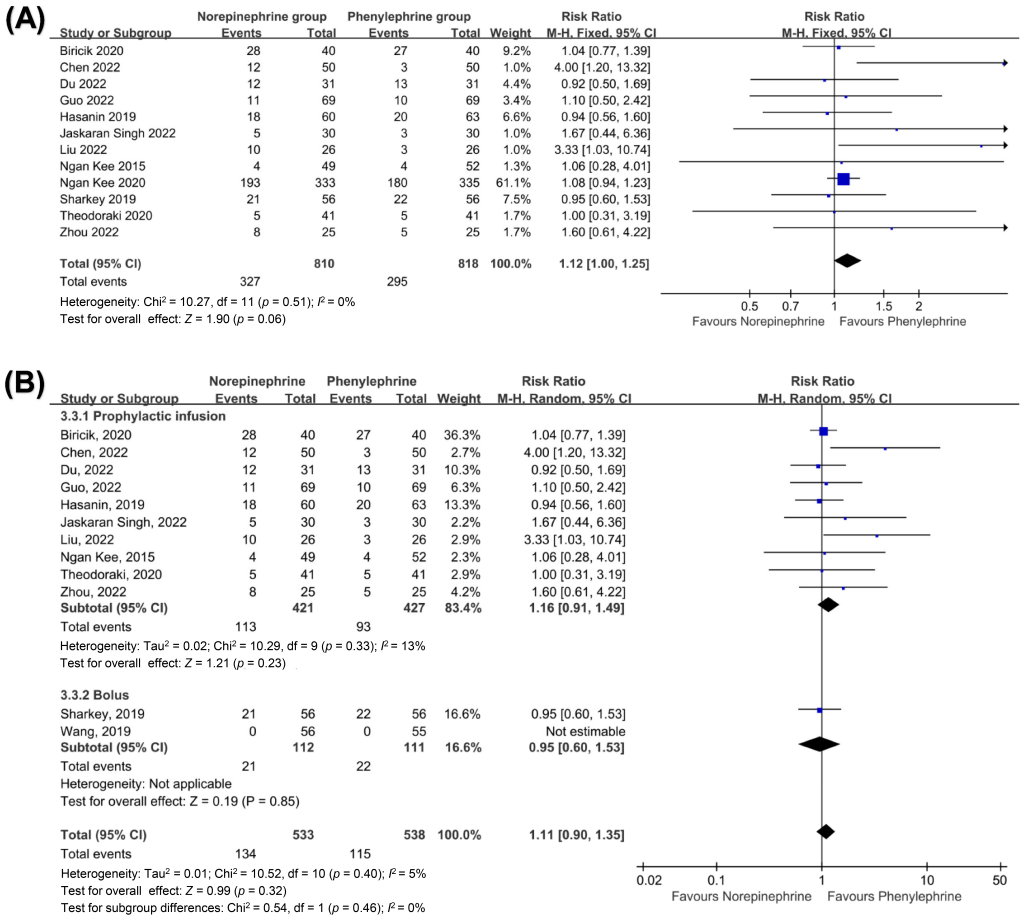

FIGURE 6. The incidence of hypotension after vasopressor-use. (A) Forest plot for maternal hypotension. (B) Forest plot for subgroup analysis of maternal hypotension. CI: confidence interval; SD: standard deviation.

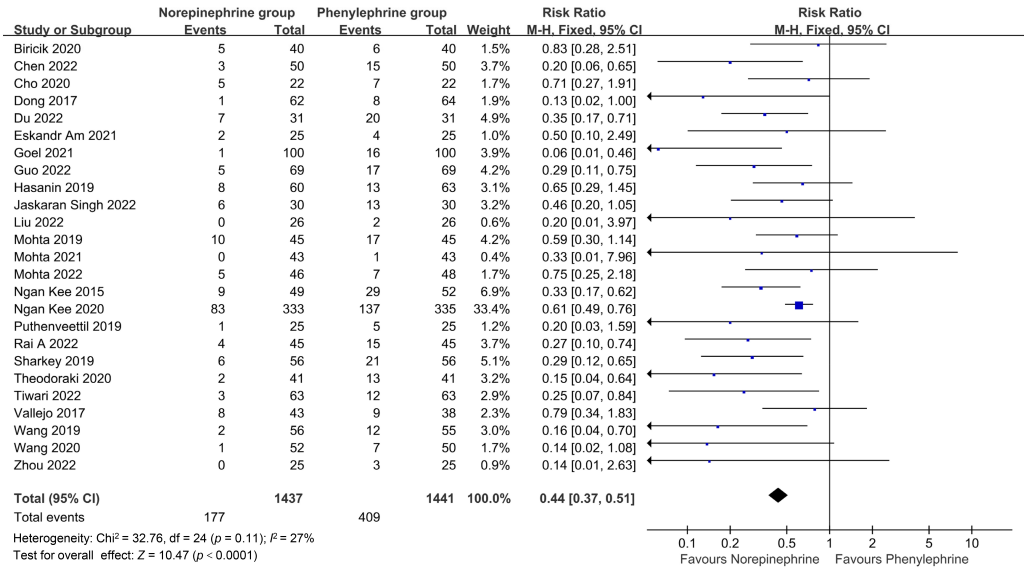

FIGURE 7. Forest plot for maternal bradycardia. CI: confidence interval.

3.5.3 The incidence of reactive hypertension

13 studies involving 1304 parturient women reported reactive hypertension after norepinephrine or phenylephrine administration. According to the meta-analysis, reactive hypertension incidence was not significantly different between these 13 studies, with a RR (95% CI) of 0.53 (0.39 to 0.72; $p < 0.001$) (Fig. 9). There was no subgroup effect related to drug administration mode ($p = 0.89$). Neither the prophylactic infusion group (RR 1.86, 95% CI 1.30 to 2.67, $p < 0.001$) or the bolus group (RR 1.67, 95% CI 0.38 to 7.29, $p = 0.50$) showed a significant difference (**Supplementary Fig. 8**).

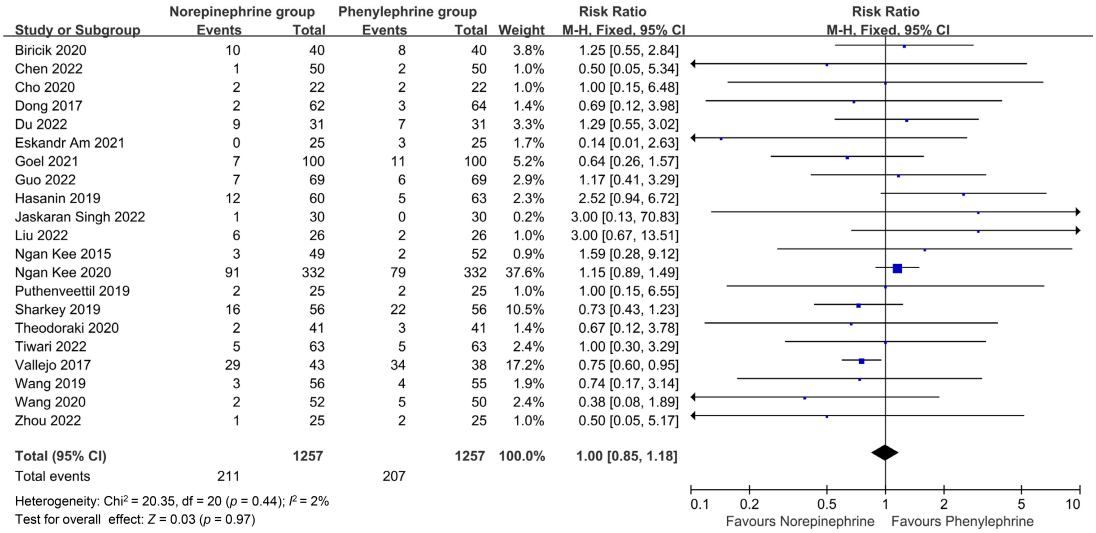

FIGURE 8. Forest plot for maternal nausea or vomiting. CI: confidence interval.

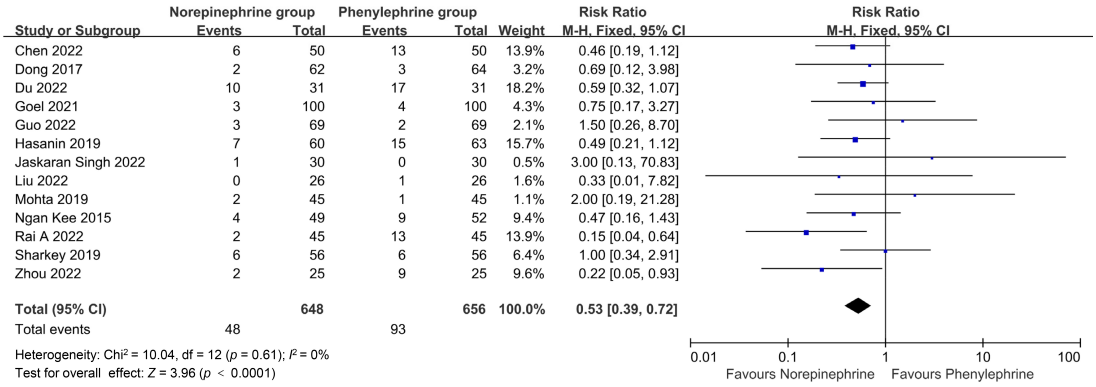

FIGURE 9. Forest plot for maternal reactive hypertension. CI: confidence interval.

4. Discussion

In this meta-analysis, norepinephrine did not significantly differ from phenylephrine for maternal hypotension after spinal anesthesia in umbilical cord blood acid-base status and APGAR scores at 1 minute and 5 minutes. Norepinephrine may also be effective in treating hypotension and exhibit fewer side effects, such as bradycardia and reactive hypertension.

Umbilical blood acid-base status and Apgar scores at 1 minute and 5 minutes for neonates were not statistically different. Despite the importance of maternal hypotension for a fetus, it has not been extensively studied. Spinal hypotension during cesarean delivery has been reported to affect neonatal acid-base balance [41, 42], with neonatal acid-base status serving as a surrogate marker of neonatal well-being. For this meta-analysis, the primary outcome was umbilical artery pH, which is the most commonly used measurement of acid-base imbalances. Based on a systematic review involving 481,753 neonates with known umbilical cord blood gases, a low arterial pH is strongly associated with long-term adverse outcomes [43]. However, there is a lack of clarity about the precise pH threshold for adverse neonatal outcomes with some studies suggesting a pH range of 7.26–7.30 is optimal for the lowest risk of adverse outcomes [44]. Norepinephrine and phenylephrine groups in this meta-analysis had mean umbilical artery pH and mean umbilical venous pH exceeding 7.2 and approaching the ideal pH range. No significant differences were found in umbilical artery pH. While umbilical venous pH was significantly different between both groups, but not clinically relevant. Also, both groups did not differ significantly on other indicators of neonatal umbilical cord blood gas analysis, including PaO_2, $PaCO_2$ and BE. Therefore, norepinephrine dose is claimed to not increase neonatal acidosis incidence when used to prevent or treat maternal hypotension after spinal anesthesia compared to phenylephrine.

Due to the ongoing controversy regarding the use of vasopressors in a preventive or therapeutic capacity, a prespecified subgroup analysis of a prophylactic infusion or bolus of norepinephrine or phenylephrine was performed. In obstetric populations undergoing spinal anesthesia, prophylactic vasopressors are generally recommended by the international consensus statements [5]. When phenylephrine was administered prophylactically, a low maternal hypotension incidence was reported compared to a single bolus for treatment [45]. However, the prophylactic administration of phenylephrine is considered too aggressive by some, potentially causing reactive hypertension and bradycardia [46]. In this meta-analysis, a significant difference was not observed between subgroups for umbilical artery pH and maternal hypotension and maternal

bradycardia, nausea, vomiting and reactive hypertension. This finding aligns with Heesen's 2014 meta-analysis, despite their smaller sample size [45]. Although our meta-analysis incorporates a large number of trials, the bolus group for maternal hypotension in the subgroup analysis only includes 2 studies, introducing some heterogeneity. Consequently, without conclusive evidence, prophylactic treatment is preferred, as delaying prophylactic vasopressor infusion may compromise its effectiveness in reducing hypotension incidence. Moreover, prophylactic continuous infusion combined with rescue bolus dosing maintains hemodynamics more effectively than rescue dosing alone [47].

Our investigation demonstrates that norepinephrine has a comparable effect on hypotension after spinal anesthesia to phenylephrine, particularly concerning maternal circulation, confirming earlier studies [30, 35, 40]. During cesarean section anesthesia, it is crucial to consider the adverse effects of drugs on the newborn and to ensure maternal circulation stability. This study assessed short-term outcomes, specifically umbilical cord blood gas analysis and APGAR scores. The long-term impact of various vasoactive drugs on neonatal prognosis remains uncertain. For instance, the establishment of early fetal gut flora might be influenced by altered placental blood supply [48]. Research focusing on the fetal implications of anesthetic management of cesarean sections is essential in the future.

In this review, maternal and neonatal outcomes following cesarean sections are comprehensively evaluated. Furthermore, eligibility criteria, data extraction, and outcome evaluation were all conducted in duplicate, demonstrating high inter-rater agreement. To adjust for potential confounders, prespecified subgroup analyses and sensitivity analyses were conducted. In addition, this review included the largest number of RCTs on this subject, achieving optimal information size and allowing for more reliable conclusions. Lastly, the I^2 statistic revealed no significant statistical heterogeneity.

Nevertheless, this meta-analysis has some limitations. We included 26 studies involving various scenarios, including healthy singleton pregnancies, parturient women with pre-eclampsia, fetal compromise, and healthy twin pregnancies. As a result of limited relevant data, certain critical variables, such as norepinephrine or phenylephrine concentration, prophylactic infusion rate, single bolus dose, and norepinephrine and phenylephrine equivalent dose ratio, may contribute to clinical heterogeneity across trials. Parturient women's CO and stroke volume (SV), which are more accurate hemodynamic indicators, were not evaluated. The effect of fluid administration on maternal circulatory stability was also not considered. Currently, circulation monitoring for cesarean sections is constrained. Cesarean section anesthesia quality and safety may be enhanced by incorporating non-invasive cardiac monitoring or real-time ultrasonic dynamic monitoring. Lastly, no long-term outcomes for newborns were assessed in our analysis due to the lack of relevant indicators in the included trials. A key evaluation metric remains improving perioperative safety and accelerating postoperative recovery.

5. Conclusion

This meta-analysis comprehensively assessed norepinephrine's efficacy in managing maternal hypotension during cesarean section under spinal anesthesia, focusing on neonatal acidemia and maternal hypotension correction. Comparing perioperative norepinephrine with phenylephrine in 2984 patients, we found no evidence of fetal acidosis associated with norepinephrine administration for maternal hypotension. Norepinephrine may also be more effective than phenylephrine in managing maternal hypotension and providing excellent maternal hemodynamic stability. However, the potential risk of norepinephrine-induced maternal reactive hypertension should not be ignored. Findings were specific to women without comorbidities. Therefore, it is crucial to evaluate the health conditions of both the mother and the fetus before selecting between the two drugs. Further studies evaluating the safety of norepinephrine and phenylephrine in managing post-anesthesia hypotension in women undergoing cesarean section should be conducted in high-quality clinical settings.

AVAILABILITY OF DATA AND MATERIALS

Data of this study can be requested through the Zigong Fourth People's Hospital by E-mail (muguo@zg120.cn).

AUTHOR CONTRIBUTIONS

JLS and GM—conceptualization and literature search, manuscript preparation and revision. GM—methodology, study supervision and article final permission. JLS and XX—trial selection. JLS and XY—data analysis. QL and BL—data extraction. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

All the authors declare that there was no conflict of interest. All authors and sponsors agreed to this publication.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1777217407638487040/attachment/Supplementary%20material.docx.

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