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Comparison of vasopressors for management of hypotension in high-risk caesarean section under neuraxial anesthesia: a systematic review and network meta-analysis

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Abstract

Background Vasopressors are effective in managing perioperative hypotension in high-risk parturients undergoing Caesarean section (CS). Nevertheless, the optimal vasopressor for addressing hypotension induced by neuraxial anesthesia remains a subject of investigation.

Methods We compared hypotension episodes among high-risk parturients who received ephedrine, noradrenaline, or phenylephrine by searching four electronic databases and reviewing the relevant references. Inclusion criteria encompassed randomized controlled trials directly comparing two or more vasopressors in the context of managing hypotension in high-risk parturients undergoing neuraxial anesthesia for CS. A network meta-analysis was performed using fixed-effects and Bayesian random-effects models.

Results We analyzed 13 trials involving 1,262 patients. While our direct and indirect comparisons revealed no reveal statistically significant differences in the number of hypotensive episodes among patients treated with different vasopressors, vasopressors were hierarchically ranked. Phenylephrine (Rank of the best choice = 0.81) exhibited the highest effectiveness in preventing hypotension, followed by ephedrine (Rank of the best choice = 0.10) and noradrenaline (Rank of the best choice = 0.09). Bradycardia occurrence was higher in patients administered phenylephrine compared to those given noradrenaline (risk ratio [RR]: 0.23; 95% confidence interval [CI]: 0.03 to 0.85) or ephedrine (RR: 0.01; 95% CI: 0.00 to 0.12). Notably, patients treated with phenylephrine or noradrenaline experienced reduced occurrences of nausea or vomiting compared to those who received ephedrine (RR: 0.37; 95% CI: 0.19 to 0.59 for phenylephrine and RR: 0.28; 95% CI: 0.10 to 0.75 for noradrenaline). Regarding fetal outcomes, no significant differences were noted between noradrenaline and phenylephrine. Overall norepinephrine in maternal outcomes may be more favorable.

Conclusions Our findings suggest the potential advantages of phenylephrine for reducing hypotensive episodes in high-risk parturients undergoing CS. Noradrenalin may emerge as an alternative, particularly for women at high risk of caesarean delivery.

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Trial registration This systematic review was registered at PROSPERO (CRD42023397259).
Keywords Blood pressure, Fetal outcome, High-risk caesarean section, Maternal outcome, Vasopressor

Background

Neuraxial anesthesia is the preferred choice of anesthesia for cesarean Sect. [1]. However, it could decrease systemic vascular resistance and cardiac output (CO), leading to hypotension in 70–90% of cases [2, 3]. A fall in systolic blood pressure can compromise placental perfusion, promoting conditions that may endanger fetal health. The consequences of this can be severe, particularly for patients with pre-eclampsia or those experiencing fetal distress (such as premature birth, placental insufficiency, or fetal compromise). In such cases, it is not advisable to have an abrupt decline in CO, as it increases the risk of unfavorable fetal outcomes, such as compromised umbilical artery base excess (BE) values and low umbilical artery pH.

The quest for an optimal vasopressor for managing hypotension in spinal anesthesia has remained a subject of debate. Ephedrine, for instance, has been associated with lower umbilical cord pH and an increased incidence of acidosis [4]. Alpha-adrenergic agonists have been recommended in international consensus statement [5]. Nonetheless, animal studies have raised concerns regarding phenylephrine's potential to decrease uterine placental perfusion [6]. Furthermore, the use of phenylephrine has been linked to a heightened risk of reflex bradycardia, which could result in reduced maternal CO [7]. While the precise clinical implications of bradycardia on fetal health remain uncertain, the associated outcomes are undesirable.

Most current comparative studies regarding the effects of vasopressors have focused on healthy individuals selected for elective surgery. Only a few studies have assessed maternal and neonatal outcomes in high-risk cesarean sections, and previous studies have paid little attention to maternal bradycardia. However, the occurrence of hypotension is highly dangerous for high-risk mothers, such as in the case of fetal damage; even mild adverse reactions to vasopressors can significantly affect fetal outcomes. Fetuses with impaired uteroplacental circulation may not be able to compensate for a further reduction in blood flow caused by a reduction in maternal CO due to vasoconstrictor or vasopressor treatment to the extent that it causes further fetal injury. Therefore, the choice of vasopressor in high-risk women is crucial. We reviewed the data from randomized controlled trials (RCTS) involving high-risk patients undergoing cesarean section. To establish a hierarchical "hierarchical order" of preference for vasoactive drugs by network meta-analysis (NMA), including indirect and direct analysis methods, and to provide valuable resources for clinical decision making.

Methods

This systematic review was conducted following a pre-established program in the PROSPERO Registry (CRD42023397259). The meta-analysis was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [8]. The results of the systematic review are reported according to a systematic review of web meta-analyses and the PRISMA inventory (Supplemental Table 1) [9].

Search strategy

Two reviewers (S-YZ and QC) independently conducted a systematic electronic literature search of the MEDLINE, Emabse, Web of Science, and Cochrane Library databases to identify relevant articles published up to February 8, 2023. We employed a combination of subject terms and free words in our search strategy, utilizing the following terms: "vasoconstrictor agents," "vasopressor," "ephedrine," "phenylephrine," "norepinephrine," "high-risk pregnancy," "fetal compromise," "emergency," and "preeclampsia," among others. A detailed explanation of the search strategy is provided in Supplemental Table 2. We also retrieved the bibliographies related to potentially relevant clinical practice guidelines [5] and systematic reviews [10–12]. The language of publication was limited to English. The final list of eligible studies was determined by discussion and consensus, and disagreements were resolved through consultation with a third adjudicator (KW).

Inclusion and exclusion criteria

Our study included RCTs comparing the utilization of two or more vasopressors for managing hypotension in high-risk parturients undergoing cesarean delivery. High-risk cesarean sections were indicated for conditions such as preterm birth, fetal compromise, placental dysfunction, pre-eclampsia, uterine placental insufficiency, or other emergencies. No restrictions were imposed based on race, age, or disease severity. The interventions involving drug administration were not constrained by dosage, regimen, dosing frequency, route, or duration.

Following the Patient Intervention Comparison Outcome framework, the inclusion criteria were as follows. Patients: women undergoing spinal anesthesia for high-risk cesarean section, including cases of preterm birth, fetal impairment, placental dysfunction, emergency, pre-eclampsia, or uterine placental insufficiency.

Interventions: administration of vasopressors to prevent or treat hypotension induced by spinal anesthesia. Comparisons: Evaluation of outcomes resulting from the administration of different vasopressors to prevent or treat spinal anesthesia-induced hypotension. Outcomes: maternal outcomes included the number of hypotensive episodes (primary outcome) and the incidence of bradycardia and nausea or vomiting. Fetal outcomes included umbilical artery BE values, umbilical artery pH, incidence of fetal acidosis, and 1-min and 5-min Apgar scores.

The exclusion criteria were as follows: studies involving non-high-risk patients undergoing cesarean section, animal trials, review articles, conference abstracts, retrospective studies, case reports, non-randomized studies, replication studies, and research involving duplicate datasets.

Data extraction

Two reviewers (S-YZ and P-PQ) independently extracted the data from the eligible trials based on predesigned tables, which included the author's name, year and journal of publication, age and number of patients, the definition of hypotension and bradycardia, route of administration and dose of antihypertensive drugs, salvage treatment with atropine, and primary and secondary outcomes. Finally, a crosscheck was performed, and any disagreements were resolved by a third reviewer (KW).

Risk of bias assessment

The methodological quality of the studies was assessed using the Cochrane Risk of Bias Tool. We assessed random sequence generation, allocation concealment, blinding of participants and healthcare providers, reported losses, selective reporting, and other biases to determine if there was a low, unclear, or high risk of bias [13]. Disagreements were resolved through discussions with a third author (KW).

Statistical analysis

Paired meta-analysis

Traditional paired meta-analysis was performed Review Manager 5.4.1 software. For dichotomous variables, the results were expressed as the risk ratio (RR) with 95% confidence interval (CI). Standardized mean difference (SMD) with 95% CI was used for continuous variables to represent the combined results. We calculated the median, interquartile range (IQR), or *P* value for continuous variables without a direct mean or SMD [14]. We used Cochrane's Q statistic (based on the chi-square test) [15] and the I^2 index [16] to evaluate homogeneity, with $P<0.1$ and $I^2>50\%$ indicating substantial heterogeneity among studies. For the fixed effects model, the differences between studies were only caused by sampling error, with little variability across studies. In the random-effects model, the variability of each study is large, which implies that the variation within each study is included, and each study has its corresponding overall effect. The pooled effect size of meta-analysis is the weighted average of multiple different population parameters. The specific calculation formulas used in these two models are different, aiming to make the meta-analysis results more credible and more accurate to express the actual effects [17]. Therefore, fixed-effects model was used in cases where heterogeneity was not significant. In cases of significant heterogeneity, a random-effects model was used for the paired meta-analysis, and a sensitivity analysis was performed to determine the source.

Network meta-analysis

The network was mapped, and the NMA was performed using Stata 16.0 and Aggregate Data Drug Information System (ADDIS) 1.16.5 software, respectively. The ADDIS analysis included modeling of "consistency" and "inconsistency." When a closed loop was available, the node-splitting method was used for inconsistency testing to determine whether the direct and indirect comparisons were consistent [18], with $P>0.05$ indicating consistency between the interventions using the consistency model. Conversely, $P<0.05$ indicated that the direct and indirect comparisons were inconsistent between the interventions using the inconsistency model. If splitting the model to test the result index was impossible, an inconsistent model was used for the analysis. Consistency models assessed the effect sizes and calculated rankings among the intervention groups. All analyses were run using four Markov chains with 20,000 tuning, 50,000 simulation iterations, thinning interval of 10, and 10,000 inference samples [19]. Convergence was monitored using trace plots and Brooks-Gelman-Rubin statistics. A potential scale reduction factor (PSRF) was used to evaluate the model convergence. If the PSRF value was close to 1, the model convergence was determined to be good, and the results were considered stable and reliable. If the PSRF score was <1.2, the convergence was considered acceptable [20]. Stata 16.0 software was used to generate funnel plots to qualitatively examine whether publication bias existed when the cumulative number of eligible studies for individual comparisons exceeded 10 [21].

Sensitivity analysis

The "leave-one-out" approach led to the exclusion of a 2008 study when assessing the robustness of the findings.

Subgroup analysis

Subgroup analysis was conducted according to the drug use in the included literature, such as population (emergency surgery or preeclampsia), duration of use

(treatment or prevention), mode of use (intravenous bolus or pump), and different doses of the three drugs.

Quality of evidence

Two reviewers (S-YZ and LL) used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to assess the quality of evidence for the estimates derived from the network meta-analyses [22]. The GRADE approach initially considers all observational studies as evidence of low quality. Of the eight criteria outlined in the GRADE method, five can diminish confidence in the accuracy of effect estimates, leading to downgrading as follows: risk of bias, inconsistency in results across studies, indirectness of evidence, imprecision, and publication bias. Additionally, three criteria are proposed to enhance confidence or upgrade it as follows: a substantial effect size with no plausible confounders, a dose-response relation, and a conclusion that all plausible residual confounding would further support inferences regarding exposure effect [23]. We arrived at an overall judgment that considered the evidential certainty in all areas, reducing the evidence by one if an area was rated as "some concern" and by two if an area was rated as "major concern". Finally, an overall qualitative judgment was made to classify each comparison based on the four levels of evidential certainty (high, medium, low, and very low).

Findings

Study selection and characteristics

Of the 2,696 records initially identified, 13 RCT [24–36], involving 1,262 patients were included in the NMA. Figure 1 illustrates the literature screening process and outcomes. Three vasopressors––phenylephrine, ephedrine, and noradrenaline––were evaluated. The fundamental characteristics of each study are summarized in Table 1. No statistically significant differences in basic characteristics were observed among the study groups. All studies, with the exception of the three-arm study conducted by Wang et al. [35], were two-arm studies. The mean sample size was 97, with a range of 20–204 participants. Six and seven RCTs provided data for the primary outcome (number of hypotensive episodes) and at least one of the secondary outcomes, respectively. Phenylephrine was the most frequently used intervention, followed by ephedrine, with 13 and 10 treatment groups, respectively. The most common route of vasopressor administration was intravenous injection ($n=9$), followed by a combination of intravenous injection and infusion ($n=4$). Most of the RCTs involved patients with pre-eclampsia ($n=8$), while the remaining studies focused on fetal injury ($n=3$) and emergency cesarean sections ($n=2$). All of the studies except one used 0.75% hyperbaric bupivacaine [28] used 0.5% hyperbaric bupivacaine, mostly 2-2.2 ml, 3 studies used 2ml [24, 25, 29],1 study used 2.4ml [28], and 1 study used 2.5ml [36]. Seven studies used adjuvants [24–29, 34], while the remaining studies did not. Among the adjuvants used, most studies used fentanyl, one used morphine [25], and one study used fentanyl plus morphine [28]. Four studies [31–33, 35] mentioned according to the height adjusting local anesthetics capacity. Five studies [26, 27, 33, 33, 36] had puncture levels at L3-4, four studies [24, 28, 29, 34] were at L3-L4 or L4-L5, three studies [30, 32, 35] were at L2-3 or L3-4, and one study [25] was at L4-5. There were no differences in demographic aspects among all articles.

Quality assessment

A quality assessment of the included studies was conducted based on the available information. We verified the deployment of a randomization protocol in each study. However, one study did not provide a clear description of how the randomization was carried out. Furthermore, two articles did not explicitly state the methods used for allocation concealment (Figs. 2 and 3).

Direct meta-analysis results

Table 2 presents the forest plot displaying the primary and secondary outcome measures, with statistically significant results highlighted in bold text.

Primary outcome assessment

The three drug comparisons did not yield statistically significant results. Notably, the comparison between ephedrine and phenylephrine demonstrated no heterogeneity among studies ($P>0.1$; $I^2<50\%$). Conversely, there was heterogeneity among studies when phenylephrine and noradrenaline were compared ($P<0.1$; $I^2>50\%$).

Secondary outcome assessments

None of the direct comparisons revealed statistically significant differences between interventions, except in five instances. The incidence of bradycardia was lower with noradrenaline than with phenylephrine ($n=4$; RR: 0.33; 95% CI: 0.18 to 0.61) and lower for ephedrine than phenylephrine ($n=6$; RR: 6.80; 95% CI: 2.69 to 17.17). The incidence of nausea or vomiting was lower with phenylephrine ($n=8$; RR: 0.50; 95% CI: 0.36 to 0.69) and noradrenaline ($n=1$; RR: 0.27; 95% CI: 0.08 to 0.91) than ephedrine. Finally, noradrenaline was superior to ephedrine in terms of the umbilical artery BE value (SMD: 1.50; 95% CI: 0.59 to 2.41).

Network meta-analysis results

Eight network diagrams were generated, which are shown in Fig. 4. Node-splitting models were employed to assess inconsistencies by testing the differences between direct and indirect effects. No significant inconsistencies were

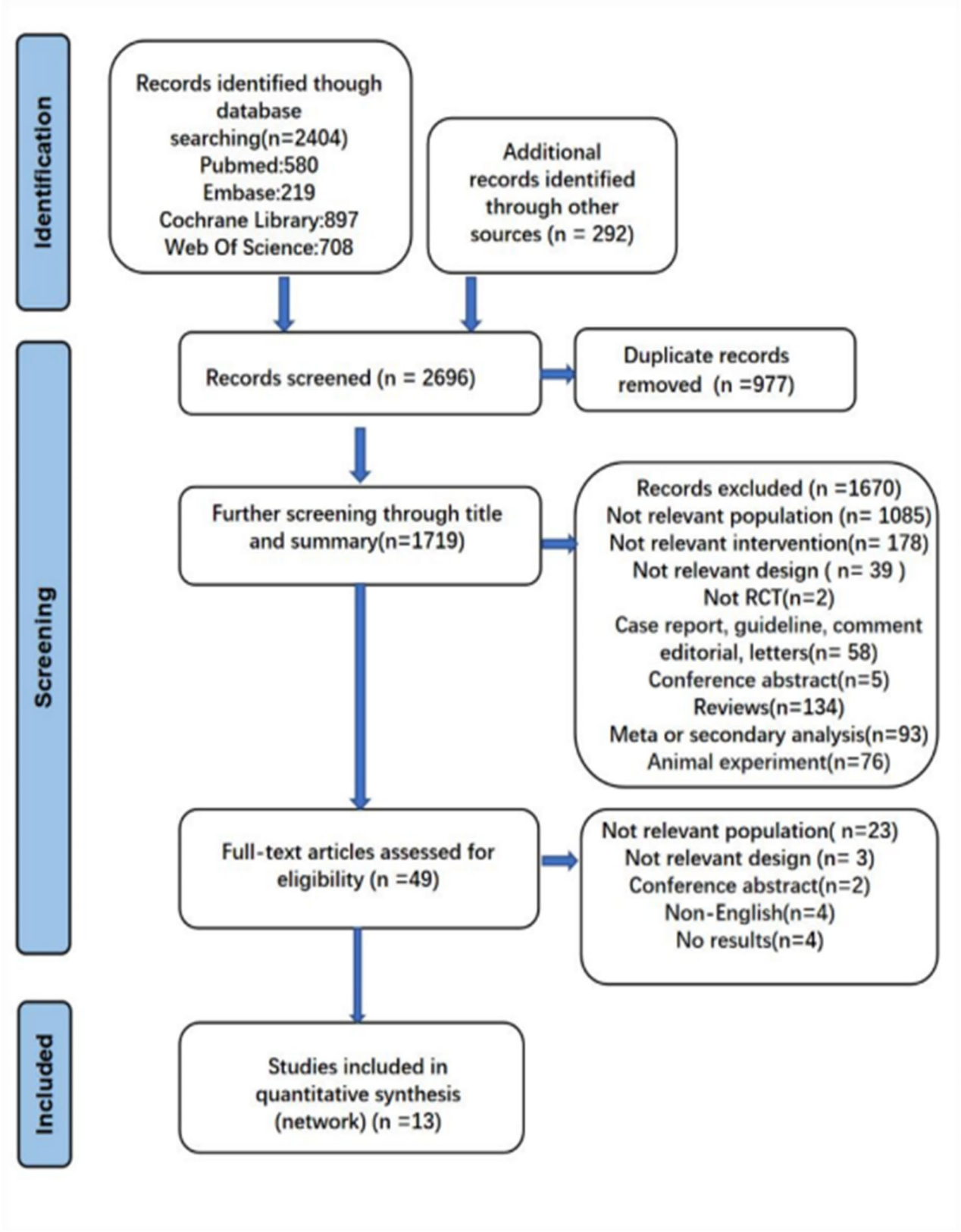

Fig. 1 Flow diagram of the literature review
The preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram of search results

Table 1 Characteristics of included randomized controlled trials

Author/Year	Country	Compared (sample size)	Initiation of vasopressor	Vasopressor regimen	Anesthesia	Vasopressor regimen	C-sections included	Definition of hypotension	Definition of bradycardia
Abdalla 2014 [25]	Egypt	Ephedrine (20) vs. Phenylephrine (20)	E: 6 mg as bolus in case of hypotension P: 75 ug as bolus in case of hypotension	Therapeutic	2 ml of hyperbaric bupivacaine 0.5% + 0.5 mg morphine Interspace: L4/5	Therapeutic	Preeclampsia	25% or more decrease in the maternal BP from baseline or SBP < 90 mmHg	Fail to mention
Dyer 2018 [26]	South Africa	Ephedrine (10) vs. Phenylephrine (10)	E: 7.5 mg P: 50 ug Doses repeated or doubled if no effect of previous dose within 60 to 90 s. If MAP < 70% from baseline immediately double dose After in total 300 ug P or 45 mg E and lack of effect the prepared alternative vasopressor could be used	Therapeutic	2.0–2.2 ml hyperbaric bupivacaine 0.5% + 10ug fentanyl. Interspace: L3/4	Therapeutic	Preeclampsia	MAP > 20% decrease from baseline or < 110 mmHg	Fail to mention
Dyer 2018 IJOA [27]	South Africa	Ephedrine (32) vs. Phenylephrine (32)	E: 7.5 mg P: 50 ug Doses repeated or doubled if no effect of previous dose within 60 to 90 s, If MAP < 70% from baseline immediately double dose After in total 300 ug P or 45 mg E and lack of effect the prepared alternative vasopressor could be used Other drugs: If HR < 55 beats/min and accompanied by hypotension (MAP < 70% from baseline), ephedrine is given 10 mg, and atropine 0.25–0.5 mg, if bradycardia persists	Therapeutic	2.0–2.2 mL of hyperbaric 0.5% bupivacaine + 10 μg fentanyl. Interspace: L3/4	Therapeutic	Preeclampsia	MAP > 20% decrease from baseline or < 110 mmHg	Fail to mention
Guo 2022 [36]	China	Phenylephrine (69) vs. Norepinephrine(69)	P:0.625 ug /k g*min N: 0.05 ug/ kg*min. If either occurred, a bolus of P (75 ug) or N (6 ug) was administered according to group allocation Other drugs: Atropine 0.25 to 0.5 mg was administered for HR < 50 beats/ min	Prophylactic	12.5 mg (2.5 ml) of hyperbaric 0.5% bupivacaine Interspace: L3/4	Prophylactic	Preeclampsia	SBP < 80% and < 60% of baseline	HR < 60 beats /min

Table 1 (continued)

Author/Year	Country	Compared (sample size)	Initiation of vasopressor	Vasopressor regimen	Anesthesia	Vasopressor regimen	C-sections included	Definition of hypotension	Definition of bradycardia
Higgins 2018 [28]	South Africa	Ephedrine (54) vs. Phenylephrine (54)	If baseline SBP was < 160 mmHg E: 8 mg/ml P: 100 ug/ml 2 ml/2 min, then BP measurement stop, if SBP > baseline or > 160 mmHg. 1 ml bolus if SBP < 80% of baseline Other drugs: Atropine 0.4 mg in case of bradycardia associated with SBP < 80% of baseline	Prophylactic	12 mg(2.4 ml) hyperbaric bupivacaine 0.75% + 15ug fentanyl + 150ug morphine Interspace: L3/4 or L4/5	Prophylactic	Preeclampsia	SBP < 80% of baseline	HR < 60 beats /min
Jain 2016 [29]	India	Ephedrine (45) vs. Phenylephrine (45)	E: 2.5 mg/min P: 30 ug/min Bolus of E: 4 mg P: 50 ug given for each hypotensive value measured Infusion stopped if SBP > 120% of baseline. Infusion reduced to half if SBP > 110% but < 120% of baseline Other drugs: Atropine 0.6 mg in case of bradycardia	Prophylactic	10 mg(2 ml) hyperbaric bupivacaine 0.5% + 25ug fentanyl. Interspace: L3/4 or L4/5	Prophylactic	Emergency cesarean section due to acute fetal compromise	SBP < 90% of baseline	HR < 50 beats/min
Mohta 2016 [30]	India	Ephedrine (53) vs. Phenylephrine (53)	E: 8 mg as bolus in case of hypotension P: 100 ug as bolus in case of hypotension Other drugs: Glycopyrronium 0.2 mg was administered for treatment of bradycardia if it was associated with hypotension or the HR < 45 beats/min irrespective of SBP value	Therapeutic	2.0–2.2 mL of hyperbaric 0.5% bupivacaine. Interspace: L2/3 or L3/4	Therapeutic	Emergency cesarean section due to acute fetal compromise	SBP < 100 mmHg	HR < 50 beats/min
Mohta 2018 [31]	India	Ephedrine (40) vs. Phenylephrine (40)	E: 4 mg as bolus in case of hypotension P: 50 ug as bolus in case of hypotension BP measured every minute, bolus given for each moment of hypotension Other drugs: Glycopyrronium 0.2 mg was administered for treatment of bradycardia if it was associated with hypotension or the HR < 45 beats/min irrespective of SBP value	Therapeutic	2.0–2.2 mL of hyperbaric 0.5% bupivacaine. Interspace: L2/3 or L3/4	Therapeutic	Preeclampsia	SBP < 80% of baseline or SBP < 100 mmHg	HR < 50 beats/min
Mohta 2021 [33]	India	Phenylephrine (43) vs. Norepinephrine(43)	P: 50 ug as bolus in case of hypotension N: 4 ug as bolus in case of hypotension Other drugs: Glycopyrrolate 0.2 mg was administered for treatment of bradycardia if it was associated with hypotension or the HR < 45 beats/min irrespective of SBP value	Therapeutic	2.0–2.2 mL of hyperbaric 0.5% bupivacaine. Interspace: L3/4	Therapeutic	Preeclampsia	SBP < 80% of baseline or SBP < 100 mmHg	HR < 50 beats/min

Table 1 (continued)

Author/Year	Country	Compared (sample size)	Initiation of vasopressor	Vasopressor regimen	Anesthesia	Vasopressor regimen	C-sections included	Definition of hypotension	Definition of bradycardia
Mohta 2022 [33]	India	Phenylephrine (50) vs. Norepinephrine(50)	P: 100ug as bolus in case of hypotension N: 8 ug as bolus in case of hypotension Other drugs: Glycopyrrolate 0.2 mg was administered for treatment of bradycardia if it was associated with hypotension or the HR < 45 beats/min irrespective of SBP value	Therapeutic	10-11 mg(2.0–2.2 mL) hyperbaric bupivacaine 0.5%. Interspace: L3/4	Therapeutic	Emergency cesarean section due to actual or potentially compromised status of the fetus	SBP < 100 mmHg	HR < 60 beats/min
Ngan Kee 2008 [34]	Hong Kong	Ephedrine (102) vs. Phenylephrine (102)	E: 10 mg as bolus in case of hypotension P: 100 ug as bolus in case of hypotension Other drugs: Atropine 0.6 mg was administered for treatment of bradycardia if it was associated with hypotension	Therapeutic	2.0-2.2mL(10-12 mg) of hyperbaric 0.5% bupivacaine. Interspace: L3/4 or L4/5	Therapeutic	Emergency cesarean section	SBP < 100 mmHg	HR < 50 beats/min
Singh 2018 [24]	India	Ephedrine (30) vs. Phenylephrine (30)	E: 8 mg/ml P: 100 ug/ml if SBP remained within 90–110% of baseline. The rate of infusion was halved (20 ml/h) if SBP was more than 110%. The infusion was stopped, if SBP was increased to more than 120% of baseline value and restarted at 40 ml/h, if SBP decreased back to between 90% and 110%. The rate was doubled (80 ml/h) if SBP was decreased to between 80% and 90% of baseline. Hypotension (SBP < 80% of baseline) was treated with 6 mg ephedrine bolus Other drugs: Bradycardia (maternal HR < 50 beats/min) if associated with hypotension was treated with 0.6 mg atropine	Prophylactic	10 mg(2 ml) hyperbaric bupivacaine 0.5% + 15ug fentanyl. Interspace: L3/4 or L4/5	Prophylactic	Emergency cesarean section	SBP < 80% of baseline	HR < 50 beats/min
Wang 2019 [35]	China	Ephedrine (55) vs. Phenylephrine (55) vs. Norepinephrine(56)	E: 4 mg as bolus in case of hypotension P: 50ug as bolus in case of hypotension N: 4ug as bolus in case of hypotension Other drugs: Intravenous atropine 0.5 mg was injected for bradycardia (HR < 60 beats/min) comorbid with hypotension, or for HR < 50 beats/min irrespective of SBP value	Therapeutic	2.0–2.2 mL of hyperbaric 0.5% bupivacaine. Interspace: L2/3 or L3/4	Therapeutic	Preeclampsia	SBP < 80% of baseline.	HR < 60 beats/min

(P = phenylephrine; N = norepinephrine; E = Ephedrine; BP = blood pressure; SBP = systolic blood pressure; MBP = mean blood pressure; HR = heart rate.)

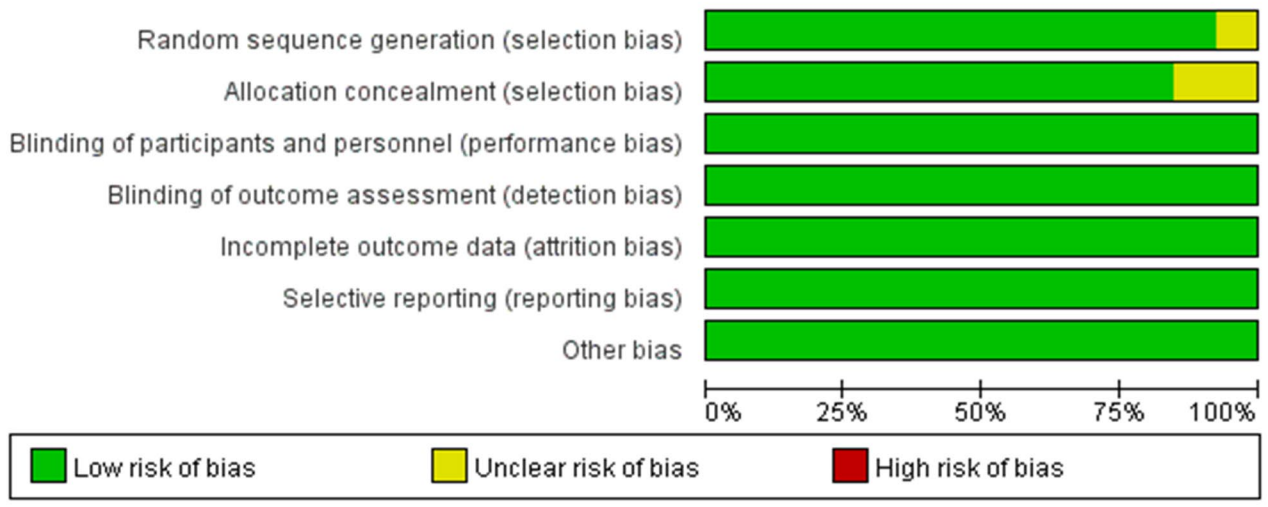

Fig. 2 Risk of bias overview
Green = low risk of bias, yellow = unclear risk of bias, red = high risk of bias

observed after constructing the model (Supplemental Table 3). Therefore, the results of the consistency model were reliable. Furthermore, the convergence of the consistency model was acceptable, with all PSRF values ≤ 1.2 for various outcome measures, including the number of hypotensive episodes, the incidence of bradycardia, the incidence of nausea or vomiting, umbilical artery BE value, umbilical artery pH, fetal acidosis, and 1-min and 5-min Apgar scores (Supplemental Table 4). Table 3 presents the complete network analysis results, with the statistically significant results indicated in bright blue. Figure 5 presents the network ranking of the primary and secondary outcome measures. All network rankings are provided in Supplemental Table 5.

Primary outcome

The NMA results revealed no statistically significant differences in the number of hypotensive episodes among the three comparisons involving the three vasopressors. The ranking of the three vasopressors from best to worst was phenylephrine > ephedrine > noradrenaline. The probability of phenylephrine being the best treatment was 81%.

Secondary outcomes

Bradycardia

The NMA results for the incidence of bradycardia revealed that ephedrine was better than noradrenaline (RR: 0.06; 95% CI: 0.00 to 0.78) and phenylephrine (RR: 0.01; 95% CI: 0.00 to 0.12), and noradrenaline was more effective than phenylephrine (RR: 0.23; 95% CI: 0.03 to 0.85). The ranking order for this variable was ephedrine > noradrenaline > phenylephrine. The probability that ephedrine is the best treatment was 98%.

Nausea or vomiting

The NMA results demonstrated that noradrenaline (RR: 3.58; 95% CI: 1.33 to 10.21) and phenylephrine (RR: 2.74; 95% CI: 1.68 to 5.21) were better than ephedrine. The rank order for this outcome was noradrenaline > phenylephrine > ephedrine, with a 71% probability of noradrenaline being the most effective.

Umbilical arterial base excess

The NMA results did not reveal significant differences in any of the comparisons. The rank order for this variable was noradrenaline > phenylephrine > ephedrine, with a 52% probability of noradrenaline being the most effective.

Umbilical arterial pH

Comparing the three drugs did not yield statistically significant differences. The rank order for this variable was phenylephrine > noradrenaline > ephedrine, with a 51% probability of phenylephrine being the most effective.

Umbilical arterial pH < 7.2

The NMA results did not show statistically significant differences in any of the comparisons. The rank order for this variable was phenylephrine > noradrenaline > ephedrine, with a 49% probability of phenylephrine being the most effective treatment.

Apgar score at 1 min

The NMA results did not reveal statistically significant differences in any of the intergroup comparisons. The rank order for this variable was noradrenaline > phenylephrine > ephedrine, with a 77% probability of noradrenaline being the most effective treatment.

Fig. 3 Risk of bias for the included studies
Green = low risk of bias, yellow = unclear risk of bias, red = high risk of bias

Table 2 Summary estimates from pairwise meta-analysis of direct comparisons

	Number of hypotensive episodes SMD (95% CI)	Bradycardia RR (95% CI)	Nausea, vomiting RR (95% CI)	Umbilical arterial BE SMD (95% CI)	Umbilical arterial pH SMD (95% CI)	Umbilical arterial pH < 7.2 RR (95% CI)	Apgar score 1 min SMD (95% CI)	Apgar score 5 min SMD (95% CI)
Noradrenaline vs. Phenylephrine	0.49 (-0.49 to 1.47)	**0.33 (0.18 to 0.61)**	1.05 (0.56 to 1.99)	0.01 (-0.43 to 0.45)	0.00 (-0.01 to 0.01)	1.07 (0.59 to 1.94)	0.35 (-0.40 to 1.10)	0.50 (-0.48 to 1.48)
Phenylephrine vs. Ephedrine	-0.06 (-0.25 to 0.13)	**6.80 (2.69 to 17.17)**	**0.50 (0.36 to 0.69)**	0.31 (-0.21 to 0.82)	0.02 (-0.00 to 0.03)	0.82 (0.60 to 1.14)	0.00 (-0.17 to 0.17)	0.00 (-0.47 to 0.47)
Noradrenaline vs. Ephedrine	0.00 (-0.39 to 0.39)	1.96 (0.18 to 21.04)	**0.27 (0.08 to 0.91)**	**1.50 (0.59 to 2.41)**	0.01 (0.00 to 0.02)	NA	0.00 (-0.52 to 0.52)	0.00 (-0.28 to 0.28)

BE, base excess; CI, confidence interval; NA, not available; RR, risk ratio; SMD, standard mean difference

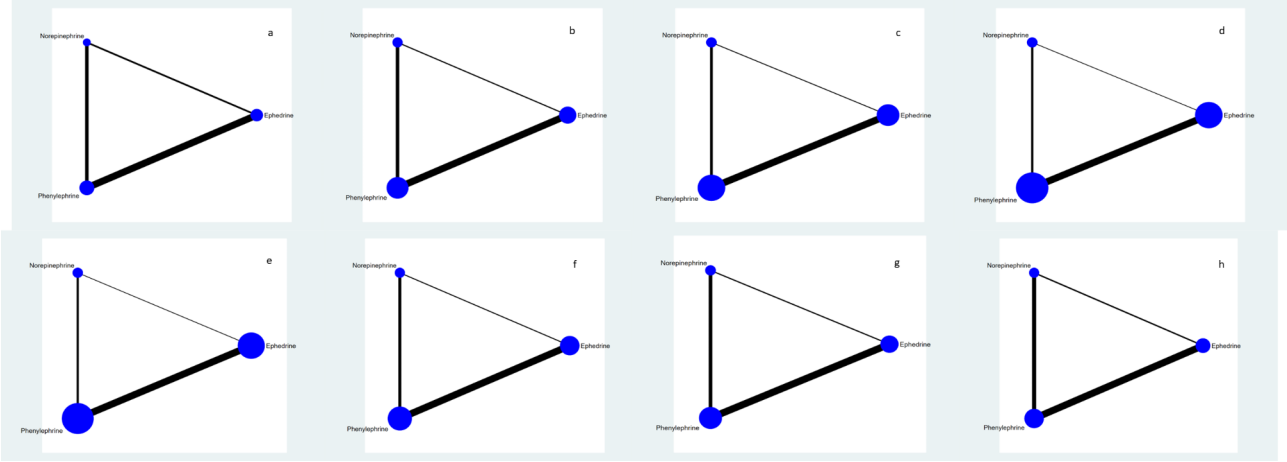

Fig. 4 Networks, point size, and treatment sample size had a positive correlation, and line thickness was proportional to the number of direct comparisons across interventions. **a**, number of hypotensive episodes. **b**, bradycardia. **c**, nausea + vomiting. **d**, umbilical arterial base excess. **e**, umbilical arterial pH. **f**, umbilical arterial pH < 7.2. **g**, Apgar score 1 min. **h**, Apgar score 5 min

Apgar score at 5 min

The NMA results did not demonstrate statistically significant differences in any of the intergroup comparisons. The rank order for this variable was noradrenaline > phenylephrine > ephedrine, with a 64% probability of noradrenaline being the most effective treatment.

Sensitivity analysis

Because uterine placental insufficiency is a major focus in studies involving fetal injury and patients with preeclampsia, we combined data from studies involving both populations. The study by Kee et al. [34], which focused on emergency cesarean sections, included women who underwent the procedure without the risk of fetal endangerment; thus, it was excluded from the sensitivity analysis. The findings of the sensitivity analysis were consistent with those of our previous studies and were considered reliable (Supplemental Fig. 2).

Subgroup analyses

We performed subgroup analyses according to patient population undergoing high-risk cesarean delivery, vasopressor use for prophylaxis or treatment, mode of administration (bolus or pump), and different dose of the drug (Supplementary Fig. 1). The results of subgroup analyses were generally consistent with those of the previous analyses.

Reporting bias

This assessment involved comparing the symmetry of the funnel plots. In terms of the incidence of nausea or vomiting, fetal acidosis, umbilical artery pH, and the 1-min Apgar score, most included studies had symmetrical distributions on both sides of the median line. This suggests a lesser likelihood that a small sample size influenced the effects. However, the incidence of bradycardia and the umbilical artery BE value were unevenly distributed on either side of the vertical median line in most studies, indicating a possible influence of small sample size (Fig. 6). Since there were fewer than 10 RCTs evaluating the number of hypotensive episodes and the 5-min Apgar score, it was not possible to assess the risk of publication bias for these variables using funnel plots.

Table 3 Network meta-analysis

Number of hypotensive	**Ephedrine**	0.20 (-0.84, 1.10)	-0.36 (-1.07, 0.27)
episodes SMD (95% CI)	-0.14 (-1.10, 0.84)	**Norepinephrine**	-0.51 (-1.42, 0.34)
	0.36 (-0.27, 1.07)	0.51 (-0.34, 1.42)	**Phenylephrine**
Bradycardia RR (95% CI)	**Ephedrine**	**16.53 (1.29,479.04)**	**75.08 (8.58,1895.48)**
	0.06 (0.00, 0.78)	**Norepinephrine**	**4.39 (1.18, 33.41)**
	0.01 (0.00, 0.12)	**0.23 (0.03, 0.85)**	**Phenylephrine**
Nausea, vomiting RR (95% CI)	**Ephedrine**	**0.28 (0.10, 0.75)**	**0.37 (0.19, 0.59)**
	3.58 (1.33, 10.21)	**Norepinephrine**	1.28 (0.55, 3.09)
	2.74 (1.68, 5.21)	0.78 (0.32, 1.81)	**Phenylephrine**
Umbilical arterial BE SMD	**Ephedrine**	0.67 (-0.47, 1.85)	0.64 (-0.00, 1.39)
(95% CI)	-0.67 (-1.85, 0.47)	**Norepinephrine**	-0.03 (-1.02, 1.03)
	-0.64 (-1.39, 0.00)	0.03 (-1.03, 1.02)	**Phenylephrine**
Umbilical arterial pH SMD	**Ephedrine**	0.02 (-0.01, 0.04)	0.02 (0.00, 0.03)
(95% CI)	-0.02 (-0.04, 0.01)	**Norepinephrine**	0.00 (-0.02, 0.02)
	-0.02 (-0.03, -0.00)	-0.00 (-0.02, 0.02)	**Phenylephrine**
Umbilical arterial pH <7.2 RR	**Ephedrine**	0.82 (0.34, 1.94)	0.78 (0.47, 1.24)
(95% CI)	1.22 (0.52, 2.95)	**Norepinephrine**	0.93 (0.44, 1.98)
	1.28 (0.81, 2.12)	1.07 (0.50, 2.26)	**Phenylephrine**
Apgar 1 min score SMD (95%	**Ephedrine**	0.30 (-0.49, 1.08)	-0.05 (-0.59, 0.52)
CI)	-0.30 (-1.08, 0.49)	**Norepinephrine**	-0.35 (-0.95, 0.28)
	0.05 (-0.52, 0.59)	0.35 (-0.28, 0.95)	**Phenylephrine**
Apgar 5min score SMD (95%	**Ephedrine**	0.21 (-0.75, 1.18)	-0.18 (-1.04, 0.71)
CI)	-0.21 (-1.18, 0.75)	**Norepinephrine**	-0.39 (-1.16, 0.41)
	0.18 (-0.71, 1.04)	0.39 (-0.41, 1.16)	**Phenylephrine**

Detailed results of network meta-analysis for bradycardia, number of hypotensive episodes, nausea + vomiting, umbilical arterial base excess, umbilical arterial pH, umbilical arterial pH < 7.2, Apgar 1 min score, Apgar 5 min score
CI = confidence interval, NA = not available, RR = risk ratio, SMD = standardized mean difference, BE = base excess

Quality of evidence

The quality of evidence for the eight outcomes was low to very low based on the GRADE evaluation tool. Most of the evidence was rated as low quality due to the risk of bias, inconsistencies, and inaccuracies (Supplemental Table 7).

Discussion

A combined systematic review and NMA was conducted to comprehensively evaluate maternal and fetal outcomes related to the prophylactic or therapeutic use of vasopressors in women undergoing spinal anesthesia for high-risk cesarean sections. Our NMA sorting results indicated that phenylephrine appears to be the optimal vasopressor for reducing hypotensive episodes. Phenylephrine and norepinephrine had similar fetal outcomes and were

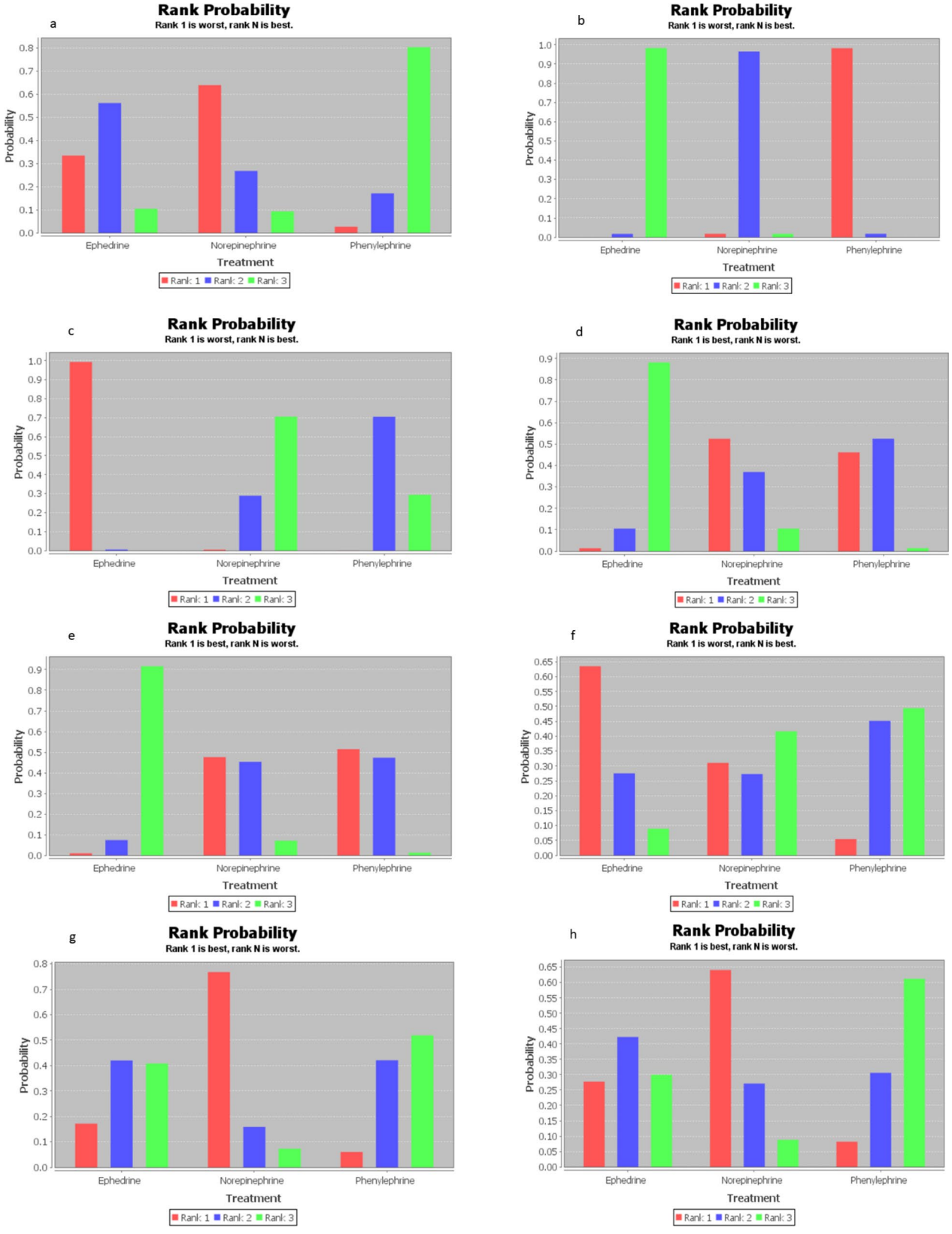

Fig. 5 Network analysis ranking map
A grid ranking: number of hypotensive episodes (**a**), bradycardia (**b**), nausea + vomiting (**c**), umbilical arterial base excess (**d**), umbilical arterial pH (**e**), umbilical arterial pH < 7.2 (**f**), Apgar score 1 min (**g**), Apgar score 5 min (**h**)

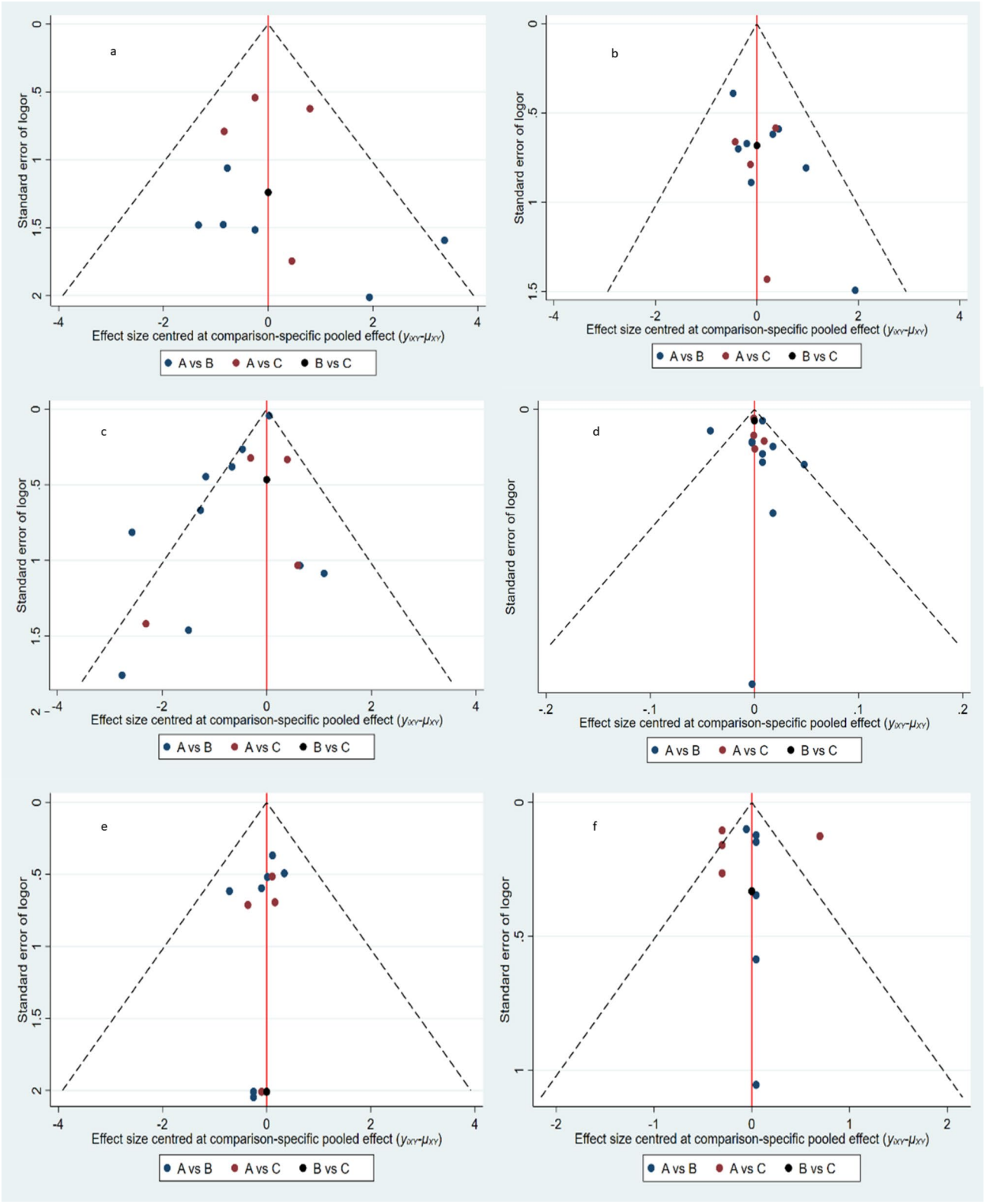

Fig. 6 Funnel diagram
Comparison-adjusted funnel plot: bradycardia (**a**), nausea + vomiting (**b**), umbilical arterial base excess (**c**), umbilical arterial pH (**d**), umbilical arterial pH < 7.2 (**e**), Apgar score 1 min (**f**)

superior to ephedrine. Noradrenaline improved maternal outcomes, such as less bradycardia and the incidence of nausea or vomiting, better than the other vasopressors. The quality of evidence in the comparison was generally low, mainly because of the inaccuracy of the test. The intervention effect estimates were robust in several preplanned sensitivity and subgroup analyses.

Previous studies have suggested that ephedrine use may be associated with more severe fetal acidosis than compared with phenylephrine [37, 38] and angiotensin II [39]. These data suggest that ephedrine may not be an ideal drug for treating hypotension in obstetric patients. Phenylephrine is a selective α1-adrenergic agonist equivalent to ephedrine for spinal hypotension [40]. Thomas et al. have shown that phenylephrine is more effective in increasing maternal uteroplacental blood flow, increasing fetal oxygen supply, and reducing acidosis [37]. However, it has recently been found that norepinephrine, with its weak β-adrenergic and potent α-adrenergic receptor agonist activity, can reduce the incidence of maternal bradycardia [41]. It has also been shown that norepinephrine has similar effects as phenylephrine in maintaining blood pressure during CS spinal anesthesia, but has less reduction in hemodynamic variables in maintaining larger CO, inhibiting venous dilatation, and increasing venous return to the heart [42]. The incidence of hypotension is reduced due to the potent α and weakly potent β endogenous adrenergic potential of hypotension [43]. These studies, as well as the current NMA, focus on healthy patients, but there are few studies on neonates with potential or existing fetal damage. These high-risk patients are at risk for uteroplacental insufficiency, which has led to concern about possible effects of vasopressors on uteroplacental circulation. Even minor adverse reactions to vasopressors can significantly impact fetal outcomes in cases of fetal damage. Fetuses experiencing impaired uteroplacental circulation may not compensate for further reductions in blood flow due to reduced maternal CO caused by vasoconstriction or vasopressor therapy. Bradycardia has a tendency to reduce placental perfusion and may cause harm to high-risk patients undergoing cesarean delivery, so it should be treated with caution as it may have clinical significance.

Some of our findings are identical and different from previous findings on this topic. For example, Fitzgerald et al. [44] investigated the prophylactic use of vasopressors to address hypotension following elective cesarean sections and found ephedrine to be the least effective, with norepinephrine surpassing phenylephrine in efficacy. However, we examined both preventive and therapeutic use in high-risk pregnancies and found that phenylephrine was superior to norepinephrine in episodes of hypotension but inferior to norepinephrine in other outcomes. Furthermore, another meta-analysis comparing ephedrine and phenylephrine revealed no significant intergroup differences in fetal outcomes [11], which is similar to our results. Our study also indicates a similar ranking of fetal outcomes for norepinephrine and phenylephrine with the findings of Kumari et al. [45]. The distinct outcomes presented in our study might be attributed to sample size.

We found that phenylephrine-induced bradycardia during high-risk cesarean sections is higher than that of other vasopressors. In contrast to phenylephrine, norepinephrine demonstrates superior capabilities in maintaining maternal CO, which may theoretically lead to better outcomes for both the mother and fetus. Kee et al. [42]found that norepinephrine contributes to high CO, primarily due to heart rate maintenance rather than an increase in stroke volume (SV). Furthermore, we observed a decrease in postoperative nausea and vomiting in women who received norepinephrine. This could be linked to enhanced gastrointestinal perfusion. However, the impact of bradycardia on placental perfusion remains debatable. While a reduction in CO is a potential risk factor for compromising placental perfusion, most studies have not identified significant differences in fetal outcomes between the use of norepinephrine and phenylephrine [45]. Therefore, although phenylephrine may result in more frequent incidents of bradycardia, its influence on placental perfusion could be limited.

This study has several strengths. First, our literature search was comprehensive and included all relevant RCTs. Second, it is the first to evaluate outcomes using a Bayesian NMA. The GRADE system was utilized to assess the quality of the evidence, and a predefined subgroup analysis was carried out to explore potential sources of heterogeneity. Moreover, this study specifically focused on patients who had undergone high-risk cesarean sections because hypotension is likely to cause fetal harm in this patient population. The unique patient population and methodology used in this study led to findings that differ from previous reports.

Nonetheless, our study has a few limitations. First, unlike traditional meta-analyses or clinical trials, NMA heavily depends on indirect estimates, and CIs often overlap due to the wide range of values reported for each outcome variable. For example, we could not precisely evaluate various vasopressor combinations, such as ephedrine and noradrenaline, as there was only one study that directly compared these outcomes. This limitation can only be addressed by conducting RCTs of high quality in the future. Second, most of our evidence was of low quality, mainly due to the heterogeneity of the included literature. For example, the dose of bupivacaine varied. Studies have shown that the occurrence of spinal hypotension is significantly related to the dose of bupivacaine, especially ≥ 10mg [46]. In addition, some of the

studies included in our study added fentanyl or morphine to local anesthetics. Intrathecal injection of opioids can improve the quality of surgical anesthesia, but it may also cause adverse reactions such as nausea and vomiting [47]. It has previously been proposed that fentanyl increases the incidence of sympathetic block, complicating the comparison of our results with studies using intrathecal local anesthetics alone [48]. Therefore, we considered various methods of vasopressor administration, including intravenous injection, intravenous pump, different doses of the drug used, and time points of administration. Although we performed a vasopressor group analysis to reduce this heterogeneity, more research on this topic is needed in the future. Furthermore, fluid therapy varied from one study to another, which could also result in different outcomes. However, given the reported limited effects of fluid therapy on fetal outcomes [49, 50], we did not implement any specific adjustments for this factor. Regarding methodological differences, it should be noted that there is no agreed-upon definition of hypotension in the scientific literature; the incidence of hypotension varies depending on the definition used, and even slight variations in the definition can result in noticeable variations in the frequency of hypotension. This is particularly true in patients with pre-eclampsia. This may impede the advancement of this field of research and make it challenging to compare studies on hypotension treatment and prevention methods [51]. In the future, we recommend further studies to determine the optimal strategy, including bolus or pump, different doses, treatment or prophylaxis, and to explore the safety of different agents, as well as in larger study populations and obstetric patients with comorbidities.

In the context of high-risk cesarean sections, phenylephrine seems to be the optimal choice for minimizing the occurrence of hypotension. Nevertheless, when considering maternal and fetal outcomes, noradrenaline may serve as a viable alternative to phenylephrine as the primary choice. However, we do not have enough evidence to support this conclusion, and future well-organized randomized studies are needed to draw more definitive conclusions.

Abbreviations

ADDIS	Aggregate Data Drug Information System
BE	Base excess
CI	Confidence interval
CO	Cardiac output
CS	Caesarean section
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
IQR	Interquartile range
NMA	Network meta-analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSRF	Potential scale reduction factor
RCTs	Randomized controlled trials
RR	Risk ratio
SMD	Standardized mean difference

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02819-9.

Supplementary Material 1: The complement of the data in this paper. Including PRISMA NMA checklist of items to include when reporting a systematic review involving a network meta-analysis, protocol and full search strategy, assessment of inconsistency results for each outcome: from the node-splitting model, the PSRF value of all outcomes, network analysis ranking table, heterogeneity test result, I^2 and heterogeneity estimate, subgroup analysis results, pairwise Meta-analysis of sensitivity analysis and evaluation of the quality of evidence using GRADE framework.

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Author contributions
SYZ and KW conceptualize the research idea, while SYZ, KW, and QC compose the initial draft. SYZ conducts data analysis. PPQ, LL, and SYZ collaborate on the final draft. KW oversees the project, and all authors unanimously approve the publication of the current version of the article.

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Data availability
All information required is given in the text and supplementary materials, other supplementary information can be obtained upon email from the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

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Competing interests
The authors declare no competing interests.

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