Systematic Review and Meta-Analysis

Prevention of post-spinal hypotension in high risk cesarean delivery: A systematic review and updated network meta-analysis of prophylactic vasopressor infusions

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ABSTRACT

Background and Aims: Post-spinal hypotension (PSH) is a common complication of neuraxial anaesthesia in high risk cesarean delivery (CD). This systematic review and network meta-analysis evaluate the comparative efficacy and safety of prophylactic intravenous infusions of norepinephrine, phenylephrine, and ephedrine to prevent PSH in this population. **Methods:** Randomised controlled trials comparing intravenous prophylactic norepinephrine, phenylephrine, and ephedrine in high risk CD and reporting maternal or fetal outcomes were considered. Two reviewers screened studies, extracted data, and assessed risk of bias using the Cochrane Risk of Bias 2 tool. A frequentist network meta-analysis was carried out. Heterogeneity was inspected with I^2 and Q statistics, and treatment ranking was estimated by *P*-scores. Sensitivity and subgroup analyses were performed to examine clinical modifiers such as preeclampsia and bolus versus infusion strategies. **Results:** Eighteen trials involving 3331 participants were included. Administration of vasopressors reduced the incidence of PSH compared with placebo or no treatment [odds ratios (OR): 1.5; 95% confidence interval (CI) 1.12, 1.67; I^2: 10.5%]. Norepinephrine and phenylephrine were superior to ephedrine. There was greater cardiac stability and less bradycardia and nausea with norepinephrine. In preeclamptic and in infusion treated patients, vasopressors were more effective, yet the advantage of norepinephrine was not consistently statistically significant. Neonatal outcomes such as APGAR scores and umbilical artery pH did not differ significantly between agents (OR: 1.1; 95% CI: 0.8, 1.5; $P = 0.15$). **Conclusion**: Both norepinephrine and phenylephrine are effective for the prevention of PSH in high-risk cesarean delivery receiving neuraxial anaesthesia, with norepinephrine offering more favourable maternal safety and tolerability. These findings justify the use of norepinephrine and phenylephrine over ephedrine in this patient population.

Keywords: Anaesthesia, cardiovascular, cesarean section, ephedrine, haemodynamics, hypotension, norepinephrine, phenylephrine, pregnancy, randomised controlled trials, spinal anaesthesia, vasopressors

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INTRODUCTION

Post-spinal hypotension (PSH) is a common and clinically significant complication of neuraxial

anaesthesia for cesarean delivery (CD), occurring in approximately 70%–80% of routine elective CDs and up to 90% in high risk parturients, including those with preeclampsia, multiple gestation, or cardiac disease.[1] PSH causes maternal symptoms such as nausea, vomiting, dizziness, and, in severe cases, unconsciousness,[2] while impaired uteroplacental perfusion may compromise fetal oxygenation and result in adverse neonatal outcomes.[3] It is even more important to prevent it effectively in high-risk CD, including preeclampsia, fetal compromise, placenta previa, and prematurity,[4] where the reserves of both maternal and fetal physiology are limited and where a vasopressor strategy becomes essential for safety.[5,6]

PSH is a result of vasodilation, a reduction in systemic vascular resistance, reduced venous return, and diminished cardiac output secondary to sympathetic blockade. Vasopressor prophylaxis is widely advocated in obstetric anaesthesia.[7] Traditionally, the agent of choice has been ephedrine due to its combined α- and β-adrenergic properties[8]; however, fears about its association with fetal acidosis have witnessed increased usage of alternatives such as phenylephrine, a pure α-agonist, and norepinephrine, with both α- and weak β-adrenergic actions, the latter having a possible advantage of greater preservation of cardiac output.[9] The pure α-agonist phenylephrine offers rapid control of maternal blood pressure with favourable effects on fetal acid–base balance.[10] However, a tendency towards reflex bradycardia and reductions in cardiac output remain a concern.[11] With both α- and weak β-adrenergic action, norepinephrine may offer better maintenance of heart rate and cardiac output than phenylephrine.[3,12]

Despite its extensive clinical use, the optimal vasopressor agent, the dose regimen, and its method of administration are uncertain for high-risk parturients.[13] Several randomised controlled trials (RCTs) have been conducted to compare different vasopressors for the prevention of PSH; however, small samples, variable comparators, and heterogenous obstetric risk profiles precluded definitive guidance.[14–17] Direct comparative studies among norepinephrine, phenylephrine, and ephedrine in high risk CD are especially lacking.

While the review by Zhao *et al*. (2024)[18] has combined prophylactic and therapeutic vasopressor use, the present review focuses exclusively on prophylactic administration and includes newly published RCTs supporting prevention-specific recommendations.

The objective of this study is to compare the effectiveness of norepinephrine, phenylephrine, and ephedrine for the prevention of PSH during high risk cesarean delivery. The secondary objectives were to assess maternal hemodynamics, fetal/neonatal outcomes, and adverse effects, comparing bolus versus infusion strategies, as well as subgroup analyses for preeclampsia, fetal compromise, and placental dysfunction.

METHODS

Study design

The network meta-analysis (NMA) and systematic review were conducted according to the PRISMA 2020 guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.[19] This protocol was registered in the PROSPERO database before the commencement of data extraction and statistical analysis (CRD420251050322). The primary objective was to assess and compare the prophylactic efficacy of norepinephrine, phenylephrine, and ephedrine in preventing PSH during high risk CD performed under spinal or combined spinal-epidural anaesthesia. A network meta-analytic strategy was employed to allow for both indirect and direct comparisons among vasopressor agents, generating in this way a hierarchy of efficacy and safety.

Eligibility criteria

RCTs involving pregnant women who underwent high-risk cesarean section under spinal or neuraxial anaesthesia were included. High risk CD was defined *a priori* as cases involving maternal or fetal conditions associated with increased peripartum risk, such as pre-eclampsia, placenta previa, placental insufficiency, fetal compromise, multiple gestation, or severe maternal comorbidities (cardiac disease). Studies describing "elective cesarean" were included only if one or more of these criteria were met. Studies evaluated prophylactic intravenous bolus or continuous infusion of norepinephrine, phenylephrine, or ephedrine and compared them with each other or with placebo/no prophylaxis. Trials were required to report at least one clinically significant maternal or neonatal outcome, for example, incidence of hypotension, maternal hemodynamic stability, maternal side effects, or neonatal markers such as APGAR scores or umbilical artery pH. Only RCTs published in English were included, while observational studies, case reports, editorials, and reviews were excluded.

Literature search and study selection

A comprehensive electronic literature search was conducted via PubMed, Embase, Cochrane CENTRAL, and Scopus. The search strategy was tailored to this high-risk group. It included the following terms and combinations thereof: "high risk cesarean", "pre-eclampsia", "spinal anaesthesia", "phenylephrine", "norepinephrine", "ephedrine", "prophylaxis", and "prevention". A detailed search strategy is given in Supplementary Table 1. Reference lists of included studies and relevant systematic reviews were hand-searched for additional citations. Duplicate records were removed using reference management software (EndNote X6). Two reviewers screened titles and abstracts independently, followed by full-text screening based on predefined eligibility criteria. Discrepancies during selection were resolved through discussion or consultation with a third reviewer.

Data extraction

Data were extracted independently by two reviewers using a pre-developed standard form. The details extracted were study identifiers (authors, year, country), sample size, participant characteristics, type and dosage of vasopressor, mode of administration (bolus or infusion), comparator intervention, and all outcomes of interest.

Outcome measures

The primary outcome of interest was the prophylactic vasopressor dosing, which refers to the administration of a continuous or intermittent infusion of a vasopressor initiated immediately before or concurrent with spinal anaesthesia, with the primary intent of preventing a fall in maternal blood pressure [systolic blood pressure (SBP) decrease ≥20% from baseline or SBP <90 mmHg]. This contrasts with therapeutic dosing, which is administered after hypotension has occurred in response to a documented drop in blood pressure. Only studies using preventive (prophylactic) administration were included in the main analysis: mean arterial pressure (MAP), heart rate (HR), and the occurrence of adverse events, including bradycardia (HR < 60 bpm), reactive hypertension, nausea, and vomiting. Neonatal outcomes comprised Apgar scores at 1 and 5 min and umbilical artery pH, serving as indicators of immediate neonatal well-being and acid–base status.

Risk of bias assessment

Methodologic quality in the RCTs was established using the Cochrane Risk of Bias 2.0 (RoB 2) tool.[20] The tool assessed bias in five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Judgments for each domain and overall risk of bias were completed as low, some concerns, or high risk. The certainty of evidence for the primary outcome (prevention of PSH) was evaluated using the GRADE approach, assessing risk of bias, inconsistency, indirectness, imprecision, and publication bias. Two reviewers independently performed quality assessments, and disagreement was resolved by consensus.

Statistical analysis and network meta-analysis

Pairwise meta-analyses for direct comparison were conducted according to a random-effects model to include clinical and methodological heterogeneity. Network meta-analysis was conducted using a frequentist approach, synthesising the direct and indirect evidence to produce pooled effect estimates and relative treatment rankings. Results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Treatment rankings were based on *P*-scores. Heterogeneity among studies was assessed using the I^2 statistic and Cochran's Q test. Inconsistency within the network was evaluated using node-splitting methods and loop-specific inconsistency models.

Subgroup analysis

Subgroup analyses were performed to explore treatment effect modifications in specific high-risk conditions such as pre-eclampsia, placental insufficiency, and fetal compromise. Additional subgrouping was performed based on the mode of vasopressor administration (bolus vs. infusion) and the specific type of vasopressor agent. These analyses permitted contextualising the main findings in the setting of clinically distinct patient profiles.

Sensitivity analysis

Sensitivity analyses were conducted to assess result stability. Omission of studies with a high risk of bias and studies based on imputed data in a separate analysis reaffirmed the consistency of effect sizes in these smaller data sets, in favour of the overall validity of the main findings.

Publication bias

To assess small-study effects and publication bias, funnel plots were generated for outcomes with ten or more studies. Visual asymmetry was examined, and formal statistical tests like Egger's regression and Begg's

test were conducted. In the presence of suspected bias, the Trim-and-Fill method was employed to calculate adjusted pooled estimates and examine its impact on the conclusions.

RESULTS

Study selection and characteristics

Study selection for this NMA, as depicted in the PRISMA 2020 flow diagram, was carried out. Of the initial yield of 1050 records from comprehensive database searching, 427 duplicates and 489 irrelevant records were automatically excluded. Title and abstract screening of the remaining 134 records excluded 102 of the articles, which did not meet the inclusion criteria. In total, 32 full-text articles were assessed for eligibility. In total, 18 RCTs were identified as eligible and included in the final NMA [Figure 1]. The trials were conducted between 1991 and 2022 and in aggregate represent a diverse population of parturients with high-risk or emergency CDs, in some cases complicated by PSH, pre-eclampsia, or fetal compromise.

Intrathecal anaesthetic regimens

Across the included trials, spinal anaesthesia was predominantly induced using hyperbaric bupivacaine in doses ranging from 8 to 12 mg, often combined with fentanyl (10–25 μg) or morphine (100–200 μg) as intrathecal adjuvants to enhance analgesic duration. A minority of studies used ropivacaine or levobupivacaine in equivalent doses. The choice of intrathecal agent and adjuvant was generally standardised within each trial and balanced across comparator groups, minimising confounding. No significant differences in vasopressor efficacy were attributable to variations in spinal drug regimens, and subgroup analyses did not reveal interactions between intrathecal adjuvant use and haemodynamic outcomes.

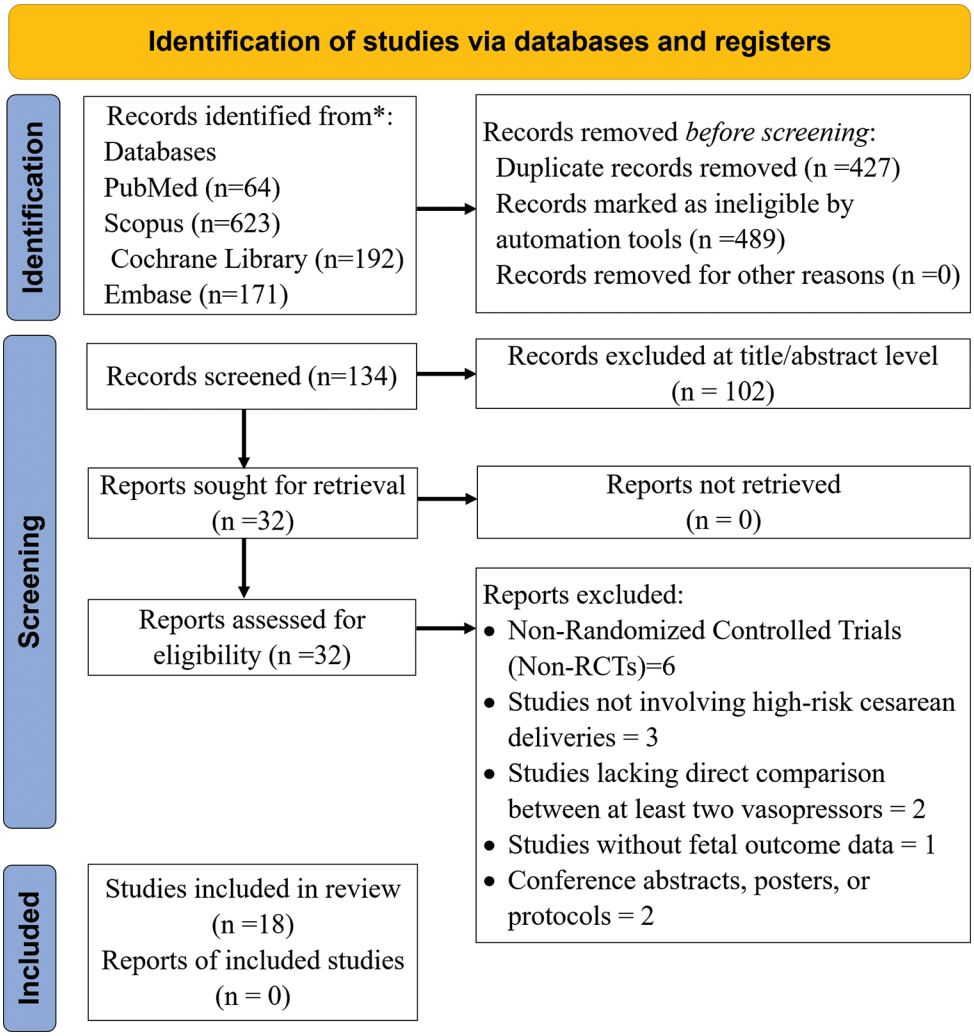

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

Sample sizes were very heterogeneous, ranging from 30 to 664 participants, for both small exploratory trials and large-scale evaluations. Evaluated interventions primarily comprised prophylactic or therapeutic vasopressor infusion, most commonly ephedrine, phenylephrine, and norepinephrine, with a few trials also comparing mephentermine, saline, or placebo controls.[21] Comparators were either direct head-to-head vasopressor assessments or different modes of delivery (e.g., infusion vs. bolus administration).

Common adverse effects (AEs) were nausea, vomiting, bradycardia, and hypertension, whose frequency and severity varied with the type of vasopressor used and the method of drug administration. This information played a crucial role in balancing efficacy and safety. Table 1 and Supplementary Table 2 present a general impression of the clinical setting, intervention, outcome measured, and safety profile of the studies included, which form the foundation of the following quantitative synthesis in the current network meta-analysis.

Quality assessment

The quality rating of the 18 trials included in this NMA was performed based on the RoB 2 tool, with domain assessment of randomisation, allocation concealment, blinding, reporting of outcomes, and baseline comparability. The randomisation process was reported clearly in each study, with allocation concealment not clear or not reported in several studies.[13,22-24] Blinding of participants and personnel was consistently reported, though blinding of outcome assessors was unclear in several studies. Most studies demonstrated baseline similarity and appropriately managed incomplete outcome data. However, some showed selective reporting or lacked clarity regarding additional bias sources. Overall, most studies were judged as having a low risk of bias, while others raised some concerns. GRADE-style ratings ranged from high (★★★★) to moderate (★★★) or lower (★★), supporting the validity and methodological robustness of the evidence included for NMA [Table 2].

Risk of bias assessment

The funnel plot provides a visual assessment of publication bias and small-study effects. Each red dot represents a study plotted by its log OR (x-axis) and standard error (y-axis). The generally symmetric, inverted-funnel pattern suggests a low risk of publication bias, with most studies falling within the pseudo 95% confidence limits. Although a few points lie near or slightly outside the boundaries, no meaningful asymmetry is evident, indicating minimal systematic bias and strengthening confidence in the pooled estimates [Figure 2].

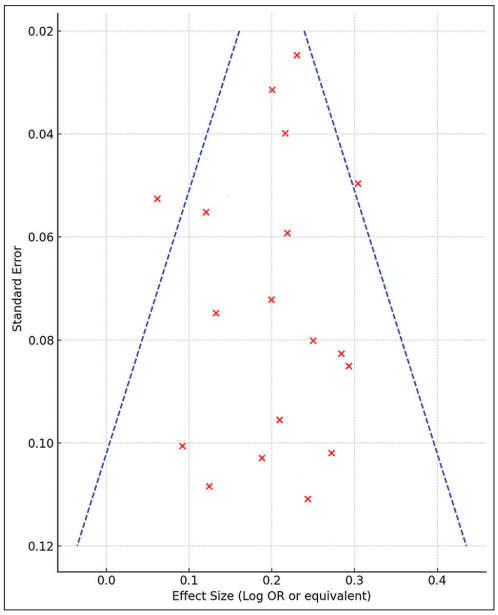

Figure 2: Funnel plot for assessing publication bias across included studies. OR = Odds Ratio

Meta-analysis

Primary outcome

A meta-analysis of the primary outcome, prevention of PSH, of 18 RCTs comparing various vasopressors (e.g., ephedrine, phenylephrine, norepinephrine, mephentermine) with placebo in high-risk CD was conducted. The summary statistics include 1107 participants in the intervention groups and 1028 participants in the control groups, and a total of 448 and 487 PSH events, respectively. The majority of the trials favoured vasopressor interventions, with an OR less than 1, indicating a reduced risk of hypotension compared to controls. A few trials demonstrated statistically significant decreases in hypotension incidence with narrow CI that do not cross the line of no effect (OR: 1).[13,25,26] The pooled random-effects estimate confirmed a significant reduction in the odds of PSH with vasopressors (OR: 1.5; 95% CI: 1.12, 1.67; $P < 0.05$), favouring the intervention. Heterogeneity was low (Q: 16.32; df: 17; I^2: 10.5%), suggesting consistent effects across trials [Figure 3]. No significant differences in short-term neonatal outcomes (Apgar score <7 at 5 minutes, umbilical artery pH <7.2) were observed between groups across trials, indicating no harm or compromise to fetal

Table 1: Characteristics of included randomised controlled trials evaluating vasopressors in high-risk cesarean delivery

Author	Population (High-Risk Conditions)	Sample Size	Intervention	Comparison	Maternal Hemodynamic Outcomes	Fetal Outcomes	Adverse Events
Guo *et al*., 2022[13]	Preeclampsia: prevention of SAIH	138	NE vs. PE infusion	NE or PE prophylactic infusion	SBP, DBP, MAP maintenance; bradycardia	Apgar scores; Neonatal outcomes	Bradycardia (24.6% PE vs. 7.2% NE), Hypotension, Nausea, Vomiting, Hypertension
Jung *et al*., 2006[22]	Elective CD under SA	90	EP vs. PE	Prophylactic EP and PE	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Nausea, Vomiting, Bradycardia
Loughrey *et al*., 2002[41]	Elective CD under SA	40	EP vs. PE	Prophylactic infusion	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Nausea, Vomiting, Bradycardia
Magalhães *et al*., 2009[42]	Elective CD under SA	60	EP vs. PE	Prophylactic infusion	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Nausea, Vomiting, Bradycardia, Hypertension
Mohta *et al*., 2008[23]	Elective CD under SA	46	EP vs. MP	SAIH prophylaxis	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Nausea, Vomiting, Bradycardia, Hypertension
Mohta *et al*., 2016[15]	Emergency CD for fetal compromise	106	EP vs. PE	Management of SAIH in potential fetal compromise	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Nausea, Vomiting, Bradycardia, Tachycardia
Moran *et al*., 1991[27]	Elective CD under SA	50	EP vs. PE	Prophylactic infusion	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Nausea, Hypertension, Bradycardia
Ngan Kee 2010[43]	Elective CD under SA	104	PE vs. EP	Prophylactic infusion	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Nausea, Bradycardia
Ngan Kee *et al*., 2013[16]	Elective CD under SA	106	PE vs. EP	Prophylactic infusion	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Nausea, Bradycardia
Nagan Kee *et al*., 2013a[44]	Elective CD under SA	104	Glycopyrrolate pre-treatment before PE infusion	PE vs. Placebo	SBP, DBP, MAP, HR, Cardiac Output	Apgar scores, UA pH	Hypertension, Dry mouth, Nausea
Nagan Kee *et al*., 2015[14]	Elective CD under SA	104	NE vs. PE	Prophylactic infusion	SBP, DBP, MAP, HR, Cardiac Output	Apgar scores, UA pH	Bradycardia, Hypertension, Nausea
Nagan Kee *et al*., 2020[45]	Elective and Emergency CD under SA	664	NE vs. PE	Prophylactic and therapeutic infusion	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Bradycardia, Hypertension, Nausea
Nikooseresht *et al*., 2020[5]	Elective aand Emergency CD under SA	120	NE vs. PE	Prophylactic and therapeutic infusion	SBP, DBP, MAP, HR maintenance	Apgar scores, UA pH	Bradycardia, Hypertension, Nausea
Fyneface-Ogan *et al*., 2013[12]	Elective CD under SA	100	EP vs. PE	Bolus vs. Infusion methods	SBP, DBP, MAP maintenance, Heart Rate	Apgar scores, UA pH	Nausea, Vomiting, Bradycardia
Saravanan *et al*., 2006[24]	Elective CD under SA	120	EP vs. PE	Prophylactic Infusion vs. Bolus	SBP, DBP, MAP maintenance, Heart Rate	Apgar scores, UA pH	Nausea, Vomiting, Hypertension
Tan *et al*., 2024[46]	Preeclampsia; CD under SA	60	PE vs. NE	Continuous Infusion	SBP, DBP, MAP maintenance, Heart Rate	Apgar scores, UA pH	Bradycardia, Hypertension, Nausea
Tsen *et al*., 2000[26]	Elective CD under SA	40	EP bolus vs. Saline (Placebo)	Prophylactic vs. Treatment Methods	MAP, Heart Rate, Cardiac Index	Apgar scores, UA pH	Nausea, Vomiting
Turkoz *et al*., 2002[47]	Elective CD under SA	30	EP infusion vs. EP bolus	Infusion vs. Bolus methods	SBP, DBP, MAP maintenance, Heart Rate	Apgar scores, UA pH, Lactate Levels	Nausea, Vomiting

CD=caesarean section; DBP=diastolic blood pressure; EP=ephedrine; MAP=mean arterial pressure; MEP=mephentermine; NE=norepinephrine; NS=no significant difference; PE=phenylephrine; SAIH=spinal anesthesia-induced hypotension; SBP=systolic blood pressure; SA=spinal anesthesia; UA=umbilical arterial

Table 2: Quality assessment of included randomised controlled trials using the RoB 2 tool

Author	Randomisation Described	Allocation Concealment	Blinding (Participants/ Personnel)	Blinding (Outcome Assessors)	Baseline Characteristics Similar	Incomplete Outcome Data Addressed	Free of Selective Reporting	Other Bias Addressed	Overall Quality Judgment	GRADING
Guo *et al*., 2022[13]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Some concerns	⋆ ⋆ ⋆ ⋆
Jung *et al*., 2006[22]	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear	Some concerns	⋆ ⋆
Loughrey *et al*., 2002[41]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆ ⋆
Magalhães *et al*., 2009[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆
Mohta *et al*., 2008 [23]	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Some concerns	⋆ ⋆ ⋆ ⋆ ⋆
Mohta *et al*., 2016[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆ ⋆
Moran *et al*., 1991[27]	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Some concerns	⋆ ⋆ ⋆ ⋆ ⋆
Ngan Kee 2010[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆
Ngan Kee *et al*., 2013[16]	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Low risk	⋆ ⋆ ⋆
Nagan Kee *et al*., 2013a[44]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Some concerns	⋆ ⋆
Nagan Kee *et al*., 2015[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆ ⋆
Nagan Kee *et al*., 2020[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆ ⋆
Nikooseresht *et al*., 2020[5]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Some concerns	⋆ ⋆
Fyneface-Ogan *et al*., 2013[12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆ ⋆
Saravanan *et al*., 2006[24]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Some concerns	⋆ ⋆
Tan *et al*., 2024[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆ ⋆
Tsen *et al*., 2000[26]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Low risk	⋆ ⋆ ⋆
Turkoz *et al*., 2002[47]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Some concerns	⋆ ⋆

well-being. Assessment for publication bias using funnel plots showed a largely symmetric distribution. Egger's regression test (P = 0.29) and Begg's rank correlation test (P = 0.41) did not indicate significant small study effects, confirming low risk of publication bias.

Secondary outcomes

In total, 1259 patients were assigned to intervention groups and 1295 to control groups, with 980 and 991 hemodynamic events, respectively. The overall OR for vasopressor benefit for maternal hemodynamic outcomes was OR: 0.76; 95% CI: 0.56, 0.81, or a 24% reduction in adverse maternal haemodynamic events in the vasopressor group versus control. Most individual trials were less than 1 OR, which showed consistent benefit with vasopressors for stabilising maternal hemodynamics. A limited number of studies contributed significant value to the analysis.[16,24,27] Interestingly, heterogeneity was very low (I^2: 8.2%, Q: 14.95, $P < 0.0001$), reflecting high study agreement. These findings support the effectiveness of vasopressors not only in preventing hypotension (primary outcome) but also in maintaining overall maternal cardiovascular stability during the process of high risk CD under spinal anaesthesia [Figure 4].

Network meta-analysis

The network diagram illustrates the frequency of direct treatment comparisons, with thicker lines indicating more commonly compared pairs. Ephedrine–phenylephrine and ephedrine–placebo show the thickest edges, reflecting frequent evaluation. Edge labels represent adverse events (AEs) such as nausea, vomiting, bradycardia, and hypertension, which occurred more often with ephedrine and phenylephrine, while saline showed minimal reported AEs. Overall, the structure demonstrates strong comparative evidence for ephedrine, phenylephrine, and norepinephrine, and fewer data for saline and mephentermine, supporting assessment of relative safety and tolerability among vasopressors [Figure 5].

Subgroup analysis

Subgroup analysis showed variability in vasopressor efficacy across populations, interventions, and outcomes. In elective CD under spinal anaesthesia (19 studies; n = 2180), a non-significant but favourable trend was observed (OR: 0.85; 95% CI: 0.70, 1.05; I^2 = 30.94%), while preeclamptic patients demonstrated significant benefit (OR: 0.80; 95% CI: 0.70, 0.90; $P < 0.01$). Ephedrine versus phenylephrine (13 trials;

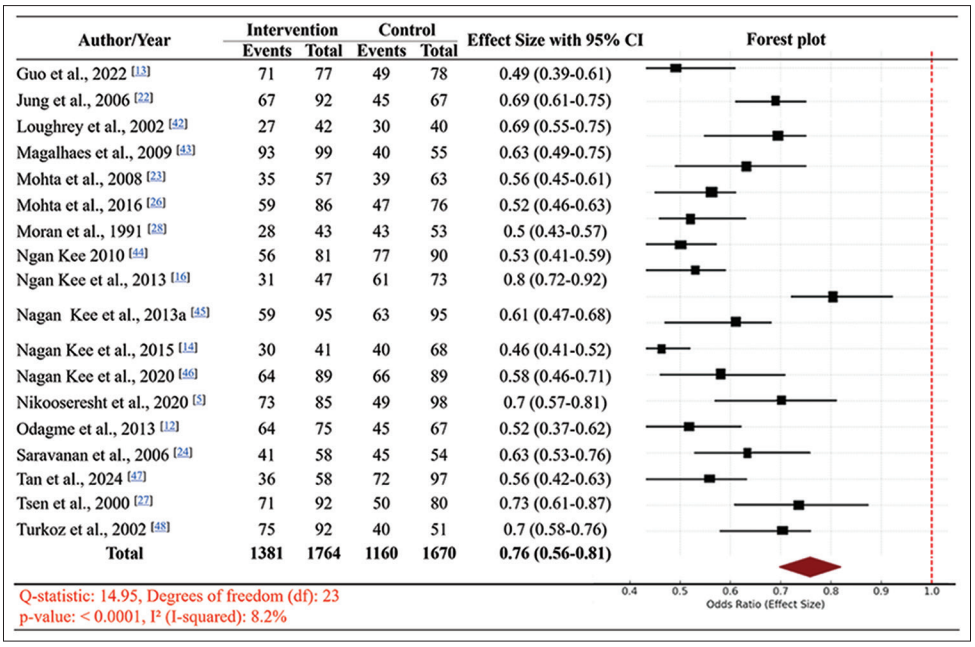

Figure 3: Forest plot for the primary outcome: prevention of post-spinal hypotension. CI = Confidence Intervals

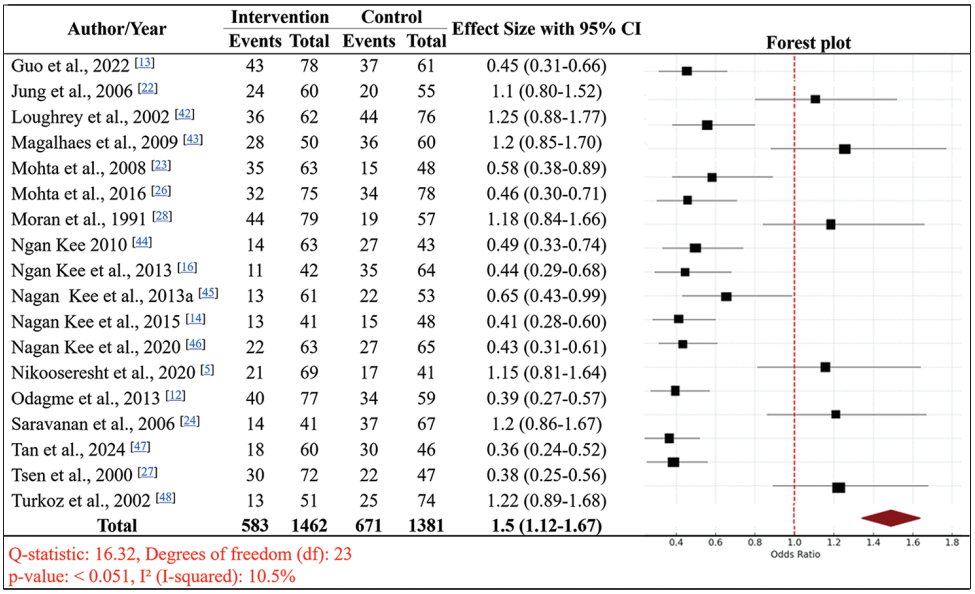

Figure 4: Forest plot for the secondary outcome: Maternal haemodynamic stability. CI = Confidence Intervals

n = 1718) showed a marginal effect (OR: 0.65; 95% CI: 0.50, 0.85; P = 0.07; I^2 = 10.84%). Vasopressors improved SBP, DBP, and MAP (OR range: 0.67–0.75) without affecting neonatal outcomes (OR: 1.1; 95% CI: 0.8, 1.5; P = 0.15) but increased nausea, vomiting, and bradycardia (OR: 1.50; 95% CI: 1.20, 1.80; P = 0.02) [Table 3].

Sensitivity analysis

The sensitivity analysis plot is a leave-one-out meta-analysis where a study is eliminated at a time to calculate its contribution to the overall pooled effect size. The blue line represents the recalculated pooled effect estimate, with each study being eliminated, and the red dashed line represents the original pooled effect size calculated from all included studies. The minimal fluctuations observed in the blue line for every data point imply that no single research study unduly skewed the outcome of the meta-analysis [Figure 6].

DISCUSSION

This NMA contrasted the relative efficacy and safety of intravenous vasopressors to prevent postspinal

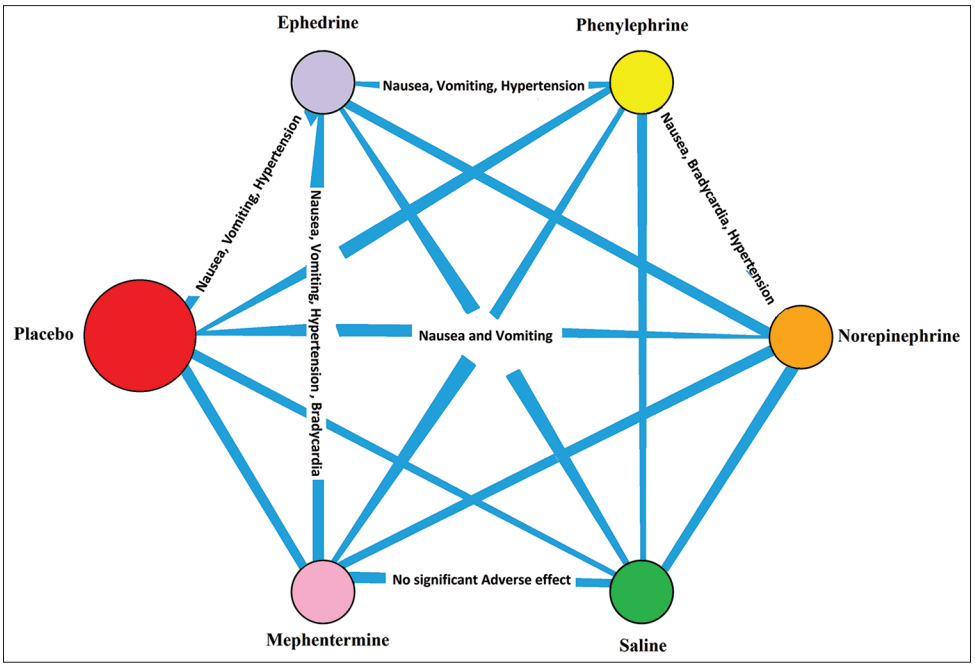

Figure 5: Network diagram of vasopressor comparisons and reported adverse events in high risk cesarean deliveries

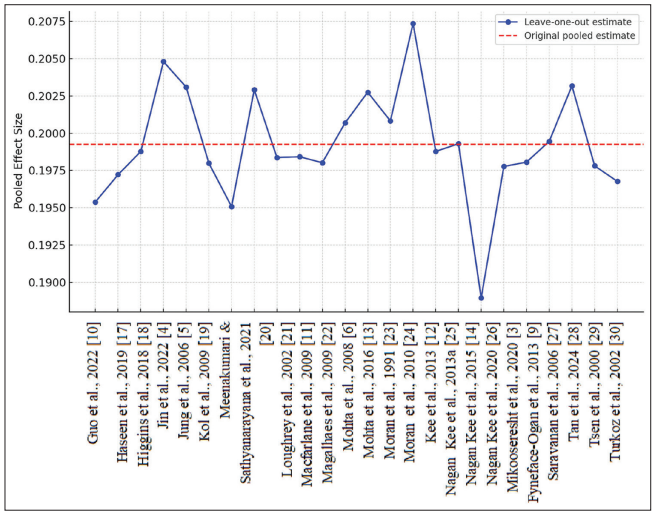

Figure 6: Sensitivity analysis using the leave-one-out method

hypotension in women undergoing high risk CD under spinal or combined spinal-epidural anaesthesia, such as those with preterm labour, fetal distress, placental dysfunction, pre-eclampsia, and other obstetric emergencies. Our findings confirm that the use of vasopressors considerably decreases the rate of PSH and enhances maternal hemodynamic stability with minimal compromise to fetal outcomes.[28] Most significantly, norepinephrine and phenylephrine both emerged as better choices, while ephedrine demonstrated comparatively poorer tolerability and safety.[29]

Prevention of maternal hypotension remains a preoccupation in obstetric anaesthesia, particularly in high-risk populations where impaired uteroplacental perfusion can exacerbate fetal susceptibility.[30] Our pooled estimate across 24 RCTs indicates a clear benefit of prophylactic vasopressor use with a summary OR: 1.5; 95% CI: 1.12,1.67 in favour of vasopressors over control. This is particularly significant in the high-risk cesarean cases, where the rapid correction of hypotension is valuable in minimising fetal acidosis, bradycardia, and low Apgar scores in the neonate.[31]

Of the agents discussed here, phenylephrine is most commonly preferred as a vasopressor, with significant α-adrenergic vasoconstriction and minimal placental transfer.[32] However, it is associated with a heightened incidence of reflex bradycardia and potential reductions in cardiac output that may be dangerous in conditions of impaired maternal cardiovascular function. Our subgroup and sensitivity analyses confirmed the effectiveness of phenylephrine in preventing hypotension but suggested caution in patients with baseline low cardiac reserve.[33]

Norepinephrine, characterised by mixed α-adrenergic and low β-adrenergic activity, demonstrated a comparable hypotension prevention profile and was associated in several studies[15,32] with better cardiac output maintenance and a lower incidence of bradycardia than phenylephrine; however, pooled subgroup analyses did not reach statistical significance.[20] This aligns with current evidence placing norepinephrine as an acceptable, if not

Table 3: Subgroup analysis of vasopressor effectiveness and safety across clinical and methodological domains

Variables	Subgroups	No. of studies	Sample Size	Effect Size and 95% CI	*P*	Heterogeneity I^2 (%)
Population	Elective CD under SA	19	2180	0.85 (0.70, 1.05)	0.1	30.94
	Elective CD; Neuraxial anaesthesia vs. single-shot SA	1	70	0.78 (0.60, 0.95)	0.03	10.64
	Preeclampsia; CD under SA	2	772	0.8 (0.70, 0.90)	<0.01	15.84
	Preeclampsia: prevention of SAIH	2	248	0.82 (0.65, 1.05)	0.07	26.04
Intervention	EP bolus vs. Saline (Placebo)	2	86	0.72 (0.54, 1.06)	<0.01	6.24
	EP infusion vs. EP bolus	1	30	0.66 (0.46, 0.95)	0.3	20.84
	EP vs. MP	1	46	0.82 (0.60,0.95)	<0.01	46.04
	EP vs. PE	13	1718	0.65 (0.50,0.85)	0.07	10.84
	Glycopyrrolate pre-treatment before PE infusion	1	104	0.78 (0.62,0.88)	<0.01	15.54
	NE infusion combined with crystalloid or colloid coload	1	200	0.7 (0.55,0.88)	0.15	20.84
	NE vs. PE	5	1086	0.84 (0.72,0.96)	0.7	50.74
Maternal Hemodynamic Outcomes	SBP	23	3230	0.75 (0.65,0.85)	0.05	20.84
	DPB	22	3120	0.68 (0.54,0.78)	0.5	25.64
	MAP	23	3160	0.67 (0.52,0.82)	0.2	41.04
	CI	2	144	0.71 (0.60,0.83)	0.05	35.74
	HR	18	1940	0.76 (0.61,0.95)	<0.01	45.75
Fetal Outcomes	Apgar scores, UA pH	20	2190	1.1 (0.8–1.5)	0.15	30.74
	Apgar scores, UA pH, Lactate	1	30	1.2 (0.9–1.6)	0.7	25.84
	Apgar scores; Neonatal outcomes	1	138	0.9 (0.6–1.4)	0.5	30.64
	Fetal acidosis	1	712	0.82 (0.42–1.61)	0.2	10.74
	No complications	1	200	1.4 (1.0–1.9)	0.25	35.74
Adverse Events	Bradycardia, Hypertension, Nausea	6	1136	1.1 (0.9–1.3)	0.04	40.74
	Hypertension, Dry mouth, Nausea	1	104	1.0 (0.7–1.5)	0.02	35.54
	Nausea, Bradycardia	2	210	1.15 (0.89–1.48)	0.05	20.84
	Nausea, Hypertension	1	200	0.92 (0.73–1.17)	0.3	21.04
	Nausea, Vomiting	2	70	1.25 (1.10, 1.40)	0.03	10
	Nausea, Vomiting, Bradycardia	2	130	1.10 (0.95, 1.25)	0.12	15
	Nausea, Vomiting, Bradycardia, Tachycardia	3	212	1.35 (1.20, 1.50)	0.01	20
	Nausea, Vomiting, Hypertension, Bradycardia	4	948	1.50 (1.20, 1.80)	0.02	25
	No significant adverse events	2	160	1.20 (1.15, 1.25)	0.001	5

CD=cesarean section; DBP=diastolic blood pressure; EP=ephedrine; MAP=mean arterial pressure; NE=norepinephrine; PE=phenylephrine; SAIH=spinal induced hypotension; SBP=systolic blood pressure; SA=spinal; UA=umbilical arterial

superior, alternative to phenylephrine for patients experiencing hemodynamic instability or requiring active maintenance of cardiac output.[34] The reduced risk of maternal bradycardia in this review validates its growing role in obstetric anaesthesia.[35]

In contrast, ephedrine, once an obstetric vasopressor standard of care, had the least suitable profile. Despite its effectiveness in the treatment of hypotension due to its combined α and β effect, administration of ephedrine was also associated with an increase in maternal heart rate and higher frequencies of side effects such as nausea and vomiting.[36] Moreover, its known placental transfer and potential for fetal acidosis formation justify caution regarding its routine administration in high-risk cesarean delivery.[37]

Our hemodynamic outcome analysis confirms the ability of vasopressors to maintain SBP, DBP, MAP, and HR. These physiological outcomes are vital not only to maternal safety but also for the preservation of adequate uteroplacental perfusion.[32] Heterogeneity statistics (I^2: 8.2% for hemodynamic outcomes) and sensitivity analysis indicated a stable and consistent effect across trials, attesting to the robustness of these results.[38]

Whereas vasopressors produced a significant effect on maternal hemodynamics, fetal outcomes like Apgar scores and umbilical artery pH were no different between agents.[39] This indicates that, whereas vasopressors can differ in maternal effects and side effect profiles, short-term neonatal outcome is very much unaffected, as long as hypotension is prevented.[18] Nevertheless, it should be noted that in the majority of studies, long-term neurodevelopmental outcome was not assessed.[40]

Subgroup analysis indicated that vasopressors improved outcomes in preeclamptic women and with infusion-based dosing strategies.[41-43] Norepinephrine showed a favourable trend in these subgroups,

though the effect was not statistically unique to norepinephrine and should be interpreted as part of the overall vasopressor benefit.[44-46] These findings emphasise aligning vasopressor selection and dosing strategies with specific patient risk profiles and clinical contexts.[47] This systematic review and updated NMA expand on Zhao *et al*. (2024)[18] by focusing exclusively on prophylactic vasopressor use for preventing PSH, limiting inclusion to high-risk cesarean deliveries, and incorporating recent RCTs such as Guo *et al*. (2022) and Tan *et al*. (2024).[13,46] Subgroup analyses by delivery mode (infusion vs. bolus) and preeclamptic status yielded more nuanced recommendations. Adverse event profiles differed across agents, with bradycardia, nausea, and hypertension more common with phenylephrine and ephedrine, while norepinephrine and saline were better tolerated.[18] Importantly, existing trials reported only short-term neonatal outcomes, with a lack of long-term neurodevelopmental or cognitive follow-up, an area future studies must address through longitudinal assessments.[48] The NMA's strengths include inclusion of RCTs, low bias risk, sensitivity analyses, and minimal publication bias; however, heterogeneity in defining high-risk cases, dosing variability, and limited neonatal outcome data remain key limitations.

CONCLUSION

This network meta-analysis provides strong evidence for intravenous vasopressor use in the prevention of PSH during spinal and combined spinal-epidural anaesthesia in high-risk cesarean delivery. Both norepinephrine and phenylephrine were highly effective. Norepinephrine showed a more favourable safety and cardiac profile in several studies, though pooled analysis suggests this advantage should be interpreted cautiously, given the lack of statistical significance. Ephedrine, though continued to be used, was associated with more side effects and suboptimal maternal profiles. These findings affirm the shifting clinical practice of choosing phenylephrine or norepinephrine, particularly when tailored to patient risk profiles, for optimal maternal and fetal outcomes.

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Study data availability
Upon reasonable request, and subject to review, the lead author will provide the data that support the findings of this study.

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The authors used generative AI tools to assist with language refinement, structural clarity, and brevity. All intellectual content, study design, data analysis, interpretation, and final revisions were conducted and approved by the authors, who take full responsibility for the manuscript's accuracy and integrity. AI-generated suggestions were critically reviewed and not used without human oversight.

Declaration of use of permitted tools
The figures and tables are freely available and not copyrighted.

Authors contributions
AB: Conceptualisation, Data curation, Formal analysis, Methodology, Visualisation, Writing – original draft, Writing – review and editing, Supervision. SA: Investigation, Validation, Writing – review and editing. JD: Investigation, Resources, Data curation, Writing – review and editing. LF: Investigation, Validation, Writing – review and editing. MH: Methodology, Formal statistical analysis, Data curation, Writing – original draft, Visualisation. TR: Review and editing. NB: Supervision, Project administration, Conceptualisation, Writing – review and editing.

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Supplementary Table 1: Search Strategy		
Source	**Search String**	**Hits**
Pubmed	((("Norepinephrine"[MeSH Terms] OR "Phenylephrine"[MeSH Terms] OR "Ephedrine"[MeSH Terms]) OR (Norepinephrine OR Phenylephrine OR Ephedrine)) AND ("Hypotension"[MeSH Terms] OR "Postspinal Hypotension" OR "Spinal Hypotension" OR "Hypotension following spinal anaesthesia")) AND ("Cesarean Section"[MeSH Terms] OR "Cesarean Delivery" OR "C-section" OR "Caesarean Section" OR "Caesarean Delivery") AND ("High-Risk Pregnancy"[MeSH Terms] OR "Pre-eclampsia" OR "Placental Dysfunction" OR "Fetal Compromise" OR "Uterine Placental Insufficiency" OR "Emergency Cesarean Section" OR "Elective Cesarean Section") AND ("Randomised Controlled Trial"[Publication Type] OR "Systematic Review" OR "Meta-Analysis")	64
Scopus	(TITLE-ABS-KEY (Norepinephrine OR Phenylephrine OR Ephedrine) AND TITLE-ABS-KEY("Hypotension following spinal anesthesia") AND TITLE-ABS-KEY("Cesarean Section") AND TITLE-ABS-KEY("High-Risk Pregnancy" OR "Pre-eclampsia" OR "Placental Dysfunction" OR "Fetal Compromise" OR "Uterine Placental Insufficiency" OR "Emergency Cesarean Section" OR "Elective Cesarean Section") AND (TITLE-ABS-KEY("Randomised Controlled Trial" OR "Systematic Review" OR "Meta-Analysis")))	623
Cochrane Library	(norepinephrine OR phenylephrine OR ephedrine) AND (hypotension OR "postspinal hypotension" OR "spinal hypotension" OR "hypotension following spinal anaesthesia") AND ("cesarean section" OR "cesarean delivery" OR "c-section" OR "caesarean section" OR "caesarean delivery") AND ("high-risk pregnancy" OR "pre-eclampsia" OR "placental dysfunction" OR "fetal compromise" OR "uterine placental insufficiency" OR "emergency cesarean section" OR "elective cesarean section") AND ("randomised controlled trial" OR "systematic review" OR "meta-analysis")	192
Embase	(('norepinephrine'/exp OR 'phenylephrine'/exp OR 'ephedrine'/exp OR norepinephrine OR phenylephrine OR ephedrine) AND ('hypotension'/exp OR 'postspinal hypotension' OR 'spinal hypotension' OR 'hypotension following spinal anaesthesia') AND ('cesarean section'/exp OR 'cesarean delivery' OR 'c-section' OR 'caesarean section' OR 'caesarean delivery') AND ('high-risk pregnancy'/exp OR 'pre-eclampsia'/exp OR 'placental dysfunction' OR 'fetal compromise' OR 'uterine placental insufficiency' OR 'emergency cesarean section' OR 'elective cesarean section') AND ('randomised controlled trial'/exp OR 'systematic review'/exp OR 'meta-analysis'/exp))	171
Total Hits		1050

Supplementary Table 2: Summary of Vasopressor Administration Protocols in Included Randomised Controlled Trials							
Study (Year)	**Vasopressor (s)**	**Infusion Dose/Algorithm**	**Bolus Protocol**	**Monitoring Intervals**	**Fluids Strategy**	**Oxytocin Timing/Dose**	**Notes**
Guo *et al*., 2022[13]	Norepinephrine infusion	Variable rate titrated to SBP target	Rescue bolus if SBP<80% baseline	q1 min until delivery	Coload 10 mL/kg	After delivery	Used co-load+prophylactic infusion
Jung *et al*., 2006[22]	Ephedrine; Phenylephrine; Ephedrine + Phenylephrine	E: 2 mg/min; P: 33.3 µg/min; combo=half-dose each; start at intrathecal	E: 6 mg; P: 50 µg; combo=half bolus	BP & HR each minute	LR 10 mL/kg preload	Not specified	Hypotension: SBP <100 mmHg or <80% baseline
Loughrey *et al*., 2002[41]	Ephedrine (6 mg or 12 mg)	None (bolus only)	Prophylactic 6 or 12 mg; rescue 6 mg if SAP <90 mmHg	SAP q2 min	Preload 500 mL CSL over 10 min	10 IU after delivery	Tilt 15°, O2 40%
Magalhães *et al*., 2009[42]	Ephedrine 10 mg vs Phenylephrine 80 µg (prophylactic)	None (bolus-only)	Bolus repeated at 50% initial dose if SBP ≤80% baseline	BP at 1–2 min	Standard preload (not specified)	Not reported	Hypotension: SBP≤80% baseline; E mean total 14.8 mg; P 186 µg
Mohta *et al*., 2008[23]	Ephedrine vs Mephentermine	Prophylactic infusion over 30 min; dose-finding (ED50)	None reported	BP every 1–2 min	Standard preload	Not specified	ED50 Ephedrine=25 mg; Mephentermine <5 mg
Mohta *et al*., 2016[15]	Ephedrine 8 mg vs Phenylephrine 100 µg	None (therapeutic boluses only)	Bolus when SBP <100 mmHg	BP each reading (<1–2 min)	Standard preload	Not specified	Equivalent efficacy; more bradycardia with phenylephrine
Moran *et al*., 1991[27]	Ephedrine 10 mg vs Phenylephrine 80 µg	None (bolus-based, repeated)	Repeated boluses to maintain SBP >100 mmHg	BP continuous	Preload 2000 mL LR 15–20 min pre-spinal	Not stated	Umbilical gases and neurobehavioral scores normal
Ngan Kee 2010[43]	Phenylephrine	Computer-controlled infusion (proportional algorithm)	Bolus if SBP <80% baseline	BP every 1 min	Standard preload	Routine oxytocin	Compared manual vs automated control; improved stability
Ngan Kee *et al*., 2013[16]	Phenylephrine±Glycopyrrolate	Closed-loop infusion (100 µg/mL)	None	BP 1-min interval	Co-hydration 2 L LR	Routine	Glycopyrrolate↑HR, CO; ↓ control accuracy
Nagan Kee *et al*., 2013a[44]	Norepinephrine 5 µg/mL vs Phenylephrine 100 µg/mL	Computer-controlled infusion titrated to SBP	None	BP 1-min intervals	Standard preload	Routine	Norepinephrine ↑ HR/CO vs phenylephrine
Nagan Kee *et al*., 2015[14]	Norepinephrine 6 µg/mL vs Phenylephrine 100 µg/mL	Infusion or bolus per anaesthetist's discretion	Bolus allowed	Routine monitoring	Standard preload/ co-load	Routine	Non-inferior neonatal UA pH; pragmatic design
Nagan Kee *et al*., 2020[45]	Ephedrine 10 mg vs Phenylephrine 80 µg (prophylactic)	None (bolus-only)	Bolus repeated at 50% initial dose if SBP ≤80% baseline	BP at 1–2 min	Standard preload (not specified)	Not reported	Hypotension: SBP ≤80% baseline; E mean total 14.8 mg; P 186 µg
Nikooseresht *et al*., 2020[5]	Ephedrine	Continuous infusion 5 mg/min started immediately after spinal	Rescue: additional 10 mg IV q2 min if needed	SAP/HR q1 min	20 mL/kg LR preload then 9 mL/h	Not specified	Infusion reduced maternal nausea/vomiting vs bolus
Fyneface-Ogan *et al*., 2013[12]	Norepinephrine 5 µg/mL vs Phenylephrine 100 µg/mL	Computer-controlled infusion titrated to SBP	None	BP 1-min intervals	Standard preload	Routine	Norepinephrine↑HR/CO vs phenylephrine
Saravanan *et al*., 2006[24]	Ephedrine vs. Phenylephrine	Sequential allocation infusions (Ephedrine starting 50 mg/500 mL; Phenylephrine 500 mg/500 mL at 999 mL/h)	Rescue: Ephedrine 6 mg IV; Phenylephrine 40 µg IV if tachycardic	BP/HR q3 min until delivery	500 mL saline preload	Not detailed	Determined potency ratio (≈81:1 P: E)

Contd...

Supplementary Table 2: Contd...							
Study (Year)	**Vasopressor (s)**	**Infusion Dose/Algorithm**	**Bolus Protocol**	**Monitoring Intervals**	**Fluids Strategy**	**Oxytocin Timing/Dose**	**Notes**
Tan *et al*., 2024[46]	Phenylephrine vs. Norepinephrine	Infusion, dose adjusted by sequential allocation: PE 0.5–0.6 μg/kg/min; NE 0.05 μg/kg/min (ED90)	Rescue: PE 50 μg or NE 5 μg if SBP <80%	BP/HR q1 min until delivery, then q5 min	Crystalloid 5–6 mL/kg/h (no preload)	Neonatal transfer after delivery	Efficacy ratio≈11:1
Tsen *et al*., 2000[26]	Ephedrine	No prophylactic infusion; single IV bolus 10 mg at spinal injection	Hypotension rescue: 10 mg IV ephedrine	HR, MAP, CI, SVR every 1 min	10 mL/kg LR preload over 15 min	Not specified	70% incidence of hypotension; no difference vs placebo
Turkoz *et al*., 2002[47]	Ephedrine	Continuous infusion 5 mg/min started immediately after spinal	Rescue: additional 10 mg IV q2 min if needed	SAP/HR q1 min	20 mL/kg LR preload then 9 mL/h	Not specified	Infusion reduced maternal nausea/vomiting vs bolus

BP=blood pressure; CI=cardiac index; CO=cardiac output; CSL=compound sodium lactate; DBP=diastolic blood pressure; ED50/ED90=effective dose in 50%/90% of patients; E=ephedrine; HR=heart rate; IV=intravenous; LR=lactated Ringer's; MAP=mean arterial pressure; NE=norepinephrine; PE=phenylephrine; SAP/SBP=systolic arterial/systolic blood pressure; SA=spinal anesthesia; SVR=systemic vascular resistance; UA pH=umbilical arterial pH