Maternal and fetal outcomes of phenylephrine bolus versus infusion during cesarean delivery: A systematic review, meta-analysis, and trial sequential analysis

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Abstract

Background and Aims: Phenylephrine is widely used to manage postspinal hypotension during cesarean delivery under neuraxial anesthesia. However, the optimal method of administration, bolus or infusion, remains uncertain.

Material and Methods: This systematic review and meta-analysis (PROSPERO CRD420251081996) included randomized controlled trials comparing phenylephrine bolus and infusion regimens during cesarean delivery. The primary outcome was maternal hypotension. Secondary outcomes included reactive hypertension, bradycardia, intraoperative nausea and vomiting, and neonatal outcomes such as Apgar scores, umbilical arterial pH, and paO_2. A random-effects model was used for meta-analysis, and trial sequential analysis (TSA) was performed to evaluate the robustness of the evidence.

Results: Twenty randomized controlled trials involving 2742 parturients (bolus n = 1314; infusion n = 1428) were included. Overall, there was no significant difference in predelivery hypotension between infusion and bolus regimens (RR 0.95, 95% CI 0.70–1.30; I^2 =94%). However, in a subgroup of fixed-rate infusions, a reduction in hypotension was observed compared with bolus (RR 0.73; 95% CI 0.61–0.88). Infusion was associated with a higher risk of reactive hypertension, while bradycardia and other maternal outcomes were similar. Although Apgar scores and UA pH showed minor statistical differences, all neonatal values remained within normal clinical ranges. TSA confirmed sufficient evidence only for the fixed-rate infusion subgroup; the overall pooled estimate remained inconclusive.

Conclusions: Phenylephrine infusion, particularly fixed-rate prophylactic infusion, may reduce hypotension, but the overall evidence does not demonstrate superiority over bolus dosing. Given the very high heterogeneity and increased reactive hypertension with infusion, results should be interpreted cautiously. Neonatal outcomes were clinically comparable between groups.

Keywords: Cesarean delivery, meta-analysis, phenylephrine, postspinal hypotension, randomized controlled trial, vasopressor administration

Introduction

Spinal anesthesia (SA) is the preferred method of anesthesia for cesarean delivery (CD) because of onset time, good recovery profile, and proven safety in mother and neonate.[1] SA is nonetheless frequently complicated by postspinal hypotension (PSH), which is said to occur as

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high as 80% if left untreated. PSH results from sympathetic blockade causing vasodilation with consequent decreased systemic vascular resistance and venous pooling. It can lead to maternal nausea, vomiting, dizziness, and compromised uteroplacental perfusion, which may lead to fetal acidosis or low Apgar scores.[2,3] Effective prevention and management of PSH are therefore essential for optimal maternal and neonatal outcomes.

Phenylephrine is a selective alpha-1 adrenergic agonist and, because of its potent vasoconstrictor actions, ability to raise systemic vascular resistance, and favorable safety profile, has been the preferred VP. Dosage practice includes intermittent bolus doses or continuous infusion, though practice varies institutionally and between providers.[4] While there is consensus on the efficacy of phenylephrine, whether intermittent bolus or continuous infusion is the superior administration method remains a matter of clinical debate and practice variation. Bolus administration is quick, allowing for the swift restoration of blood pressure, and it is suitable for established or prophylactic PSH treatment.[5] Fixed- or variable-rate infusions, by comparison, are meant to maintain constant plasma levels with minimal fluctuation and possibly increase blood pressure stability. Infusions, though, can have delayed therapeutic onset, require rigorous monitoring, and increase prolonged hypertension and bradycardia risks.[6,7]

Clinical practice varies considerably among institutions and regions. Surveys of obstetric anesthetic practice have shown inconsistent adoption of infusion protocols, with some centers favoring intermittent boluses due to ease of use, resource limitations, or provider preference, while others routinely employ fixed-rate infusions.[8] However, robust comparative evidence remains limited, and prior meta-analyses have yielded inconsistent conclusions.

In particular, previous meta-analyses, such as Heesen *et al.* (2014) and Garg *et al.* (2024), showed a trend toward infusion in preventing hypotension, but these were limited by significant heterogeneity, a lack of subgroup analyses according to infusion type, and the absence of TSA for testing the conclusiveness of the pooled evidence.[9,10] In the light of such limitations, the degree of certainty regarding the true superiority of infusion or bolus regimens remains undetermined. Several previous meta-analyses have assessed phenylephrine infusion versus bolus strategies, although their conclusions remain variable.

Heesen *et al.* 2014[10] pooled nine trials and reported that infusion regimens were associated with reduced maternal hypotension, but this analysis was limited by small numbers of studies, substantial heterogeneity, and the absence of trial sequential analysis to confirm evidence adequacy. The more recent Garg *et al.* 2024[9] meta-analysis, which added further trials to this analysis, also found that infusion may better prevent hypotension, but heterogeneity remained high, outcome definitions varied, and subgroup effects of fixed versus variable infusion and prophylactic versus therapeutic bolus administration were incompletely explored. Therefore, uncertainty remains about the true comparative effectiveness of infusion and bolus regimens. Compared with previous published meta-analyses on this topic, including Garg *et al.* 2024 and Heesen *et al.* 2014, our study provides several methodological and clinical advancements. Our study updates the evidence base with 20 randomized trials and is the first to apply TSA and detailed subgroup analyses to determine whether existing data are sufficient to draw firm conclusions on which administration strategies provide clinically important benefits.

Study objective and novelty

The current meta-analysis goes beyond prior studies in several ways. First, our review includes new trials that were published between August 2023 and December 2024, thus increasing the overall sample size and updating evidence not available in previous analyses. Second, we performed a different subgroup comparison—between fixed-rate and variable-rate infusion regimens—showing that only fixed-rate prophylactic infusion resulted in a uniform reduction of predelivery hypotension, whereas variable-rate infusion did not yield an important clinical difference not explored previously. Third, trials involving non-IV routes, high-risk cardiovascular patients, hypertensive disorders, or multimodal vasopressor use were excluded, thus exclusively addressing uncomplicated cesarean deliveries in healthy parturients; this further enhanced clinical homogeneity and applicability. Last but not least, while TSA was by no means a novelty, it added methodological strength in showing that overall evidence remains inconclusive despite statistically significant subgroup effects, underlining that fixed-rate infusion should be regarded as beneficial rather than definitely superior. The combination of these components yields an analysis that is more stratified, clinically relevant, and current than any presented previously.

Material and Methods

The systematic review and meta-analysis were conducted in accordance with the PRISMA 2020 guidelines which followed the PRISMA 2020 statement for transparent and complete reporting.[11] The protocol was prospectively registered in the International Prospective Register of Systematic Reviews [registration number CRD420251081996]. PRISAM checklist is provided in Appendix I.

Eligibility criteria

Included were only English-language RCTs comparing fixed- or variable-rate infusions of phenylephrine versus preventive or therapeutic boluses with cesarean delivery under spinal or combined spinal–epidural anesthesia. Excluded were non-IV administration, multiple vasopressor or phenylephrine dose comparisons, cardiovascular disease, hypertensive pregnancy disorders, postpartum hemorrhage, or insufficient outcomes (studies that lacked relevant, extractable, or group-specific maternal or fetal outcome data necessary for quantitative analysis). Preventive boluses (50–100 μg IV after SA) and therapeutic boluses (50–100 μg IV for SBP < 80% baseline) were compared with fixed-rate or variable-rate infusions titrated to maintain SBP between ±20% baseline.

Search strategy

Several databases, including the U.S. Clinical Trials Registry, Embase (via Ovid), Medline (via PubMed), and Cochrane Central Register of Controlled Trials (CENTRAL), were searched. The goal of this study was to examine the effects of phenylephrine bolus versus infusion regimes on maternal and neonatal outcomes during CD under spinal or combined spinal–epidural anesthesia. A combination of controlled vocabulary and free-text terms, including "hypotension," "cesarean," and "phenylephrine," were used in the search. The identified articles were published between 2010 and 2025. The search was conducted from June to July 2025. To identify further eligible trials, the reference lists of the included studies and review articles were manually searched. The full search strategy for at least one of the databases is documented in Appendix II.

Study selection

Two reviewers independently screened the titles and abstracts of identified studies. Full texts were obtained for articles that met the inclusion criteria or those that were unclear based on the abstracts alone. Inclusion disagreements were resolved by discussion with a third reviewer.

Data extraction

A data extraction form was developed in Microsoft Excel.[12] One reviewer extracted the data, and another reviewer confirmed that it was accurate. The year of publication, study design details, phenylephrine administration and duration, sample size, and incidence of significant outcomes, such as maternal hypotension (SBP <80% of baseline), reactive hypertension (SBP increase >20% from baseline), bradycardia (heart rate (HR) <50 bpm), intraoperative nausea and vomiting, neonatal pH, Apgar score, and fetal acidosis, were among the data that were extracted. If more data clarification was required, the authors were contacted.

Assessment of risk of bias

Using the Cochrane Risk of Bias 2.0 tool, two reviewers evaluated the possibility of bias in five areas: measurement of outcomes, randomization, variations from intended interventions, missing outcome data, and selective reporting.[13] A third reviewer settled disagreements. The overall certainty of the evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system.[14] All authors agreed on the final grades, which were assigned as follows: high (⨁⨁⨁⨁), moderate (⨁⨁⨁⊖), low (⨁⨁⊖⊖), or extremely low (⨁⊖⊖⊖).

Outcomes of interest

The primary outcome was the incidence of maternal hypotension after neuraxial anesthesia for CD. Secondary outcomes included infant outcomes (UA and UV pH, Apgar score at 1 and 5 minutes, umbilical PaO_2) and maternal side effects (reactive hypertension, bradycardia, nausea/vomiting). "Predelivery hypotension" was defined as a drop in systolic blood pressure (SBP) to less than 80% of baseline which occurred following neuraxial anesthesia but prior to fetal delivery. "Postdelivery hypotension" was the term used to describe hypotension that happens after fetal extraction, usually during oxytocin administration or uterine manipulation. Where data were available, events were grouped according to their intraoperative time, although not all publications utilized these words specifically. Although definitions of 'predelivery' and 'postdelivery' hypotension varied across studies, for consistency in data synthesis, we adopted a standardized operational approach. Where possible, we extracted outcomes defined as a ≥20% decrease in SBP from baseline and categorized them based on timing relative to fetal delivery. When exact timing was unclear, we used author definitions and performed sensitivity analyses to assess robustness.

Data synthesis and statistical analysis

Relative risk (RR) and 95% CI were used to pool dichotomous outcomes (such as incidence rates of bradycardia or hypotension), while mean differences (MDs) and 95% CI were used to pool continuous outcomes (such as pH and Apgar score). Using existing methods, studies that reported medians and interquartile ranges were transformed into estimated means and standard deviations.[15,16] The I^2 statistic was used to analyze heterogeneity. A random-effects model was used for meta-analysis. Subgroup analyses were conducted based on the type of infusion (fixed vs. variable rate) and time of bolus (prophylactic vs. therapeutic). Version 5.4.12 of the Review Manager software was used. A *P*-value of less than 0.05 was deemed significant in all two-sided statistical analyses. Meta-regression could not be performed because key covariates were inconsistently reported.

Trial sequential analysis

To enhance the conclusiveness of the findings and reduce repeated testing random error, Trial Sequential Analysis (TSA) was performed.[17] TSA provided the required information size (RIS), similar to that of a single RCT's sample size, and applied monitoring boundaries for the prophylactic and therapeutic bolus versus infusion group comparisons in preventing predelivery hypotension. Assumptions were 80% power, two-sided alpha at 5%, pooled-control event rate, and prespecified relative risk reduction, using a random-effects model. Analyses used TSA software (v0.9.5.10 Beta; Copenhagen Trial Unit, Denmark).

Results

A total of 1198 records were identified through a systematic search of PubMed, Embase, Cochrane Library, and Science Direct; 453 duplicates and 268 automatically detected records were excluded, leaving 477 records screened at the level of title and abstract. A further 427 articles were excluded at the title/abstract level, and 50 full-text articles were assessed for eligibility. Following the exclusion of nonrandomized studies, comparisons with other VPs or doses of phenylephrine, or those involving high-risk obstetric patients, 20 prospective or randomized studies were selected for the final meta-analysis [Figure 1]. The studies collectively enrolled 2742 parturients undergoing CD with spinal or combined spinal–epidural anesthesia. Sample sizes across studies ranged from 50 to 506 participants, in the bolus (n = 1314) and infusion groups (n = 1428). The studies were conducted in diverse geographic settings including India, South Africa, Canada, Brazil, Iran, Pakistan, Egypt, and Lebanon from 2010 to 2025. The phenylephrine regimens varied by dose and administration strategies—ranging from fixed bolus to titrated infusions—and outcomes comprised both maternal (hypotension, bradycardia, nausea/vomiting, and blood pressure stability) and fetal parameters (e.g., Apgar scores and umbilical blood gas values). A summary of study details is provided in Table 1.

Risk of bias assessment

As illustrated in Figure 2, random sequence generation issues were reported in two studies.[18,19] Four studies[18,20-22] had poor or no allocation concealment. Unblinding of participants and personnel resulting in performance bias was reported in six studies.[18-20,22-24] Five studies[18-20,23,24] expressed concerns about detection bias based on inadequate blinding of outcome assessors. On the other hand, all studies were graded as low risk for selective reporting and incomplete outcome data and none of the studies were graded as high risk for other biases. Overall, most included studies had a low risk of bias across important domains, supporting the reliability of the evidence base.

Quality of evidence

The quality of evidence regarding comparative effectiveness of phenylephrine bolus and infusion regimens was inconsistent, ranging from moderate for reactive hypertension and predelivery hypotension to very low for bradycardia and vomiting outcomes, largely due to imprecision and risk of bias across studies [Table 2].

Meta-Analysis

Maternal outcomes

1. **Hemodynamic Variables**

a. Predelivery Hypotension

The pooled meta-analysis of 20 studies (n = 2742) showed no statistically significant difference in overall predelivery hypotension between infusion and bolus administration (RR 0.95, 95% CI 0.70–1.30; $P = 0.45$), with very high heterogeneity (I^2 =94%), indicating inconsistency across trials [Figure 3]. This suggests that the overall evidence is inconclusive regarding superiority of either regimen. In subgroup analysis, fixed-rate infusion regimens were associated with a significant reduction in hypotension (RR 0.73, 95% CI 0.61–0.88; $P = 0.0009$; I^2 =47%), whereas variable-rate infusions and bolus regimens showed no clear advantage. High heterogeneity may reflect differences in study design, phenylephrine dosing, fluid co-loading, and definitions of hypotension [Supplementary Figure 1a]. In contrast, variable-rate infusion regimens were not superior to bolus (RR 1.14, 95% CI [0.87, 1.51], $P = 0.34$), and heterogeneity remained moderate (I^2 = 39%). Neither therapeutic nor prophylactic bolus regimens were superior to infusion when isolated. The RR for the therapeutic bolus subgroup was 1.06 (95% CI [0.72, 2.20], $P = 0.88$; I^2 = 85%), and the RR for the prophylactic bolus subgroup was 0.94 (95% CI [0.69, 1.28], $P = 0.70$; I^2 = 68%) Supplementary Figure 1b). Overall, the findings show that fixed-rate phenylephrine infusion offers the most optimal method of preventing hypotension at all stages of delivery, while other modes of administration, particularly variable infusions and boluses, result in inconsistent or suboptimal benefits.

a. Reactive Hypertension

Eight studies[4,18,19,21,23,25-27] assessed reactive hypertension, that is, a transient, compensatory elevation in blood pressure in response to VP administration. Pooled analysis revealed a significantly lower risk

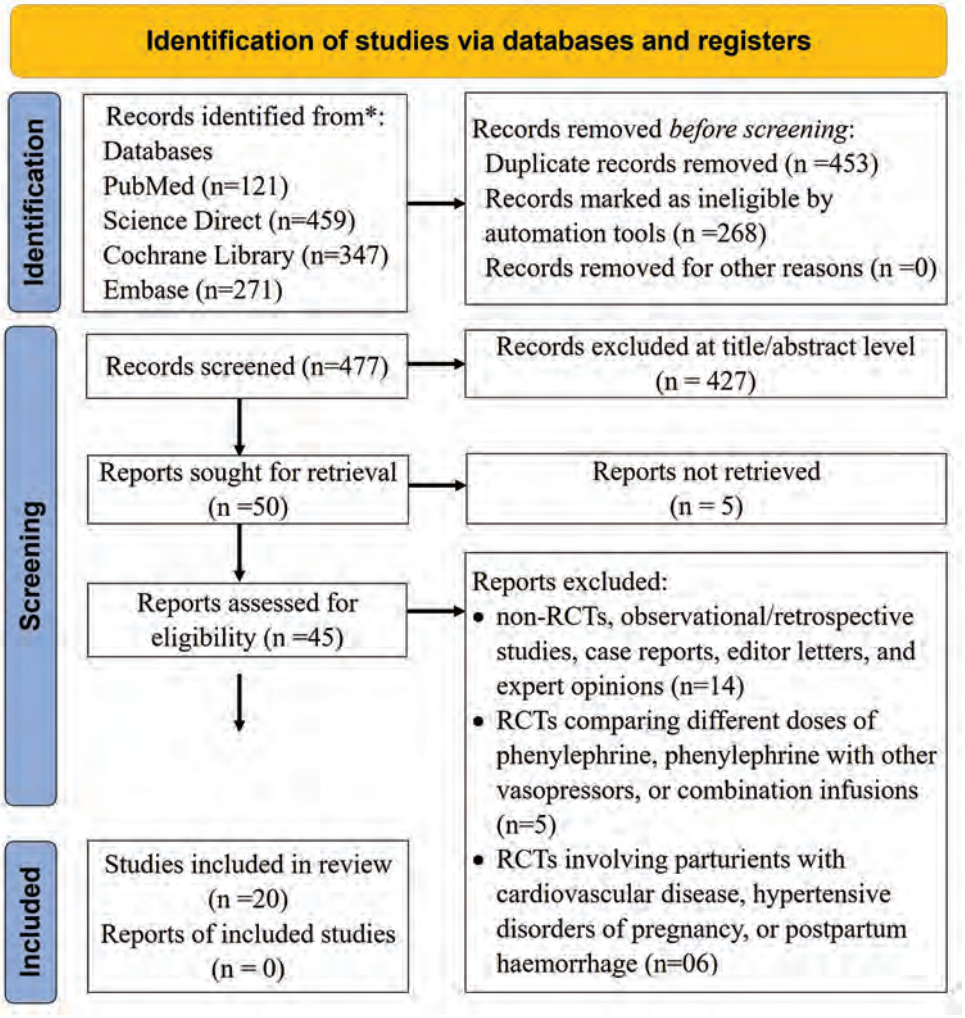

Figure 1: PRISMA 2020 flow diagram

of reactive hypertension with phenylephrine bolus compared to infusion (RR 0.58, 95% CI [0.47, 0.72], $P < 0.00001$), with moderate heterogeneity ($I^2 = 56\%$) [Supplementary Figure 2]. This finding suggests that bolus administration of phenylephrine may allow for more immediate correction of hypotension and improved treatability, thereby offering greater hemodynamic precision.

b. Postdelivery Hypotension

Eight studies[4,23,25,28-32] reported the incidence of postdelivery hypotension in comparisons with phenylephrine bolus versus infusion regimens. The meta-analysis found no significant difference between the two approaches (RR 0.95, 95% CI [0.61–1.47], $P = 0.78$), but there was high heterogeneity among the studies ($I^2 = 85\%$) [Supplementary Figure 3a]. Although some individual studies, such as Hasanin *et al.*, 2019[23] and George *et al.*, 2018[33], have reported a lower incidence of postdelivery hypotension in the infusion group, the overall findings were inconclusive. These results suggest that neither method of administration confers a clear advantage in maintaining hemodynamic stability during the postpartum period. It should also be noted that the average interval from induction of spinal anesthesia to fetal delivery typically exceeds 20 min,[34] which may reduce the sensitivity and consistency of postdelivery hypotension assessments across studies.

c. Bradycardia

Nine studies[4,18,19,23,25,26,32,35,36] reported maternal bradycardia, and the meta-analysis found no significant difference between infusion and bolus regimens (RR 0.87, 95% CI [0.69, 1.09], $P = 0.23$), with moderate heterogeneity ($I^2 = 66\%$) [Supplementary Figure 3b]. While two individual trials favored infusion, the overall effect was not significant.[23,36] Therefore, the risk of bradycardia may be related to factors other than the method of phenylephrine administration.

2. Intraoperative Nausea and Vomiting

a. Vomiting

Fourteen studies[4,19-21,23,25-28,30,31,35-37] described intraoperative

Table 1: Study and population characteristics of included trials comparing PE Bolus versus infusion

Study ID	Sample Size (*n*)	Bolus vs Infusion Group (*n*/*n*)	Groups Detail
Bishop *et al.*, 2017[18]	506	253/253	Bolus: Rescue VPs as needed. infusion: Fixed-rate PE infusion (25 μg/min) + bolus if MAP <80% baseline.
Buthelezi *et al.*, 2020[19]	300	150/150	Bolus: Intermittent PE bolus for SBP <90 mmHg. infusion: 500 μg PE in 1L Ringer's lactate as co-load + rescue bolus.
Choudhary *et al.*, 2018[20]	94	44/44	Bolus: 50 μg PE when SBP dropped ≥20%. infusion: 50 μg/min prophylactic.
de Neves *et al.*, 2010[35]	60	30/30	Bolus: 100 μg PE administered IV if SBP <80% baseline. infusion: Continuous PE at 0.25 μg/kg/min started immediately after spinal injection.
Doherty *et al.*, 2012[4]	60	30/30	Bolus: 120 μg PE intermittently. infusion: 120 μg/min fixed rate.
George *et al.*, 2018[25]	160	79/81	Bolus: 100 μg bolus as needed (*n*=79); PE infusion: started at 50 μg/min, titrated per protocol (n=81). All obese parturients undergoing C-section.
Gowtham *et al.*, 2023[32]	60	30/30	Bolus: 50 μg IV when SBP drops <20% from baseline. Repeated as needed. infusion: 50 μg/min IV started immediately post-spinal, titrated as needed.
Hasanin *et al.*, 2019[23]	217	76/141	Bolus: 1.5 μg/kg after spinal + PRN. Fixed infusion: 0.75 μg/kg/min, on-off strategy. Variable infusion: 0.75 μg/kg/min titrated.
Kulkarni *et al.*, 2021[38]	70	35/35	Bolus: PE 100 μg bolus for treating hypotension. infusion: Prophylactic PE 100 μg/min ×3 min
Kumar *et al.*, 2020[28]	60	30/30	Bolus: 50 μg bolus when SBP ↓ 20% from baseline. infusion: PE 0.5 μg/kg/min started post-SAB
Kumari *et al.*, 2021[24]	50	25/25	Bolus: 100 μg IV bolus when SAP ↓ 80% of baseline. infusion: PE 100 μg/min × 3 min post-spinal
Mahboob *et al.*, 2018[29]	70	35/35	Bolus: 50 μg rescue PE; infusion: 0.75 μg/kg/min for 5 min post SA
Mounika *et al.*, 2025[30]	60	30/30	Bolus: 100 μg PE on hypotension; infusion: 100 μg/min for 3 min post SAB, adjusted by BP
Nikooseresht *et al.*, 2020[21]	120	40/80	Bolus: 100 μg prophylactic PE; infusion: 50 μg/min continuous till delivery
Rana *et al.*, 2020[22]	80	40/40	Bolus: 50-100 μg PE rescue; infusion: 0.75 μg/kg/min variable rate with rescue bolus
Riaz *et al.*, 2024[31]	390	195/195	Bolus: 100 μg PE as needed; infusion: 100 μg/ml at 1 ml/min x 5 min, adjusted by MAP
Sen *et al.*, 2013[26]	90	45/45	Bolus: 6% HES 15 ml/kg + IV PE 50 μg intermittent bolus. infusion: 6% HES 15 ml/kg + IV PE bolus 50 μg + infusion at 60 μg/min.
Shafeinia *et al.*, 2020[37]	116	58/58	Bolus: Received NS; if hypotension occurred (>20 % drop or SBP <90 mmHg), 100 μg PE bolus given. infusion: 35 μg/min PE infusion.
Siddik-Sayyid *et al.*, 2014[27]	79	39/40	Bolus: Received 15 mL/kg Ringer's solution coload + variable rate PE infusion (starting 0.75 μg/kg/min) + rescue bolus (100 μg) as needed. infusion: Received coload + saline infusion (placebo) + PE bolus only for hypotension episodes.
Singh *et al.*, 2023[36]	100	50/50	Bolus (PB): Received 50 μg PE IV bolus when SBP dropped ≥20% from baseline. infusion (PI): Received PE 50 μg/min infusion prophylactically post-spinal block.

Prospective Single-Center Alternating Intervention (Prospective SC-AI study); Prospective Alternating Intervention (Prospective-AI study); Randomized Controlled Trial (RCT); Quasi-Experimental (QE); Double-Blind Randomized Controlled Trial (Double-blind RCT); Observational Comparative (OC); Phenylephrine (phenylephrine); Systolic Blood Pressure (SBP); Diastolic Blood Pressure (DBP); Mean Arterial Pressure (MAP); Heart Rate (HR); Apgar Score (Apgar)

vomiting, and meta-analysis indicated a nonsignificant trend toward increased vomiting with bolus versus infusion (RR 1.58, 95% CI [0.96, 2.59], $P = 0.069$), with high heterogeneity (I^2 =87%) [Supplementary Figure 4a], although two studies[24,31] reported an increased incidence with the use of bolus and two studies reported no apparent difference. Given the very high heterogeneity, results should be interpreted cautiously. Variations in outcome definitions and anesthetic techniques likely contributed to inconsistency across studies.

b. Nausea

The incidence of nausea from ten studies[19,20,23,25,28,30,31,35-37] did not show any statistically significant difference between phenylephrine infusion and bolus (RR 1.26, 95% CI [0.72, 2.20], $P = 0.42$), with significant heterogeneity (I^2 =86%) [Supplementary Figure 4b]. The high I^2 value suggests marked variability across trials, possibly due to differing definitions of nausea, anesthetic adjuncts, and coadministered fluids. Two studies[19,30] demonstrated a similar or slightly increased risk of

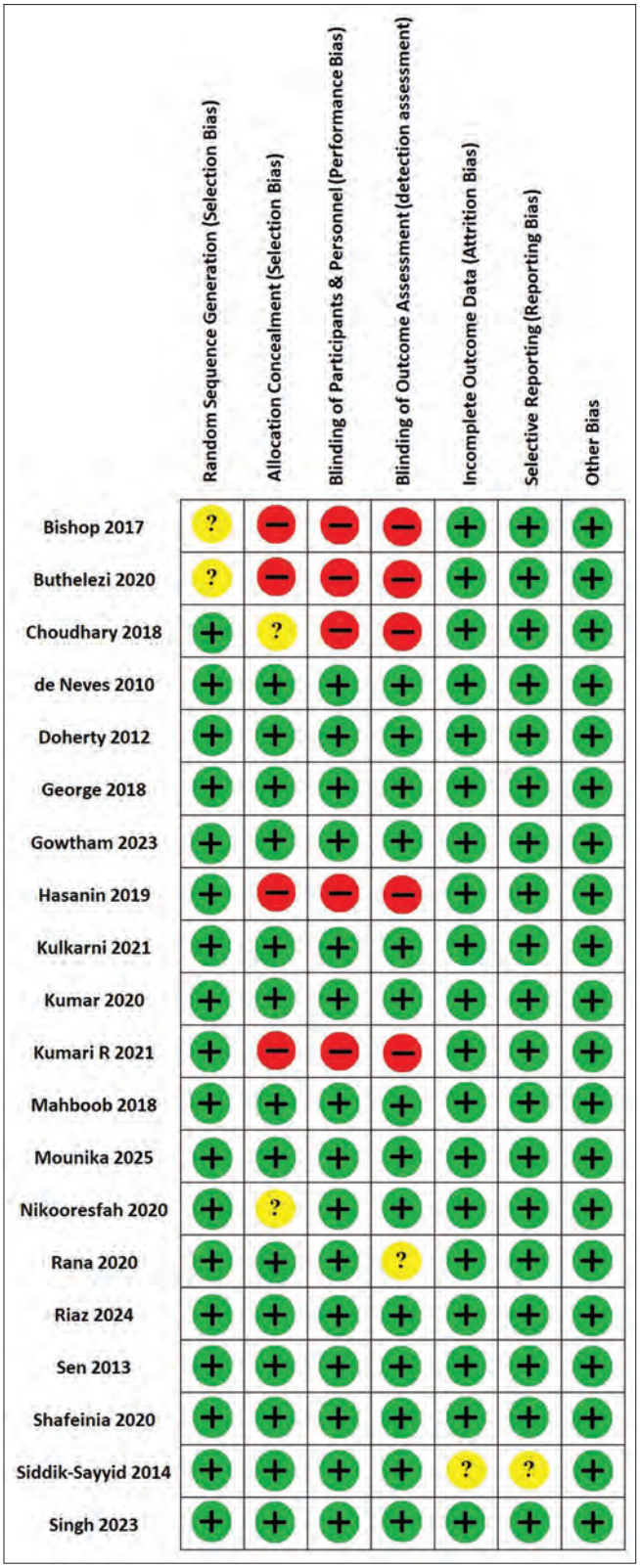

Figure 2: Summary of Risk of Bias for Included Studies Comparing Phenylephrine Bolus and Infusion Regimens During CD

nausea with bolus administration; however, a wide CI and inconsistent findings highlight the uncertainty of this association. The overall pooled data did not demonstrate a clear benefit of either bolus or infusion in the prevention of intraoperative nausea and vomiting.

Neonatal Outcomes

1. APGAR

Ten studies[19,21,23,24,27,28,30,32,36-38] reported Apgar scores. While a statistically significant mean difference at 1 minute favored bolus administration (MD 0.50; 95% CI 0.19–0.81), both groups maintained median Apgar scores ≥7, indicating no clinically relevant impact on neonatal status. Similarly, the small difference in UA pH (MD –0.03) favored infusion but remained within normal physiological limits, confirming no neonatal acidemia and no need for intervention [Supplementary Figure 5]. Two studies[23,36] reported higher mean scores in the bolus group, although the difference was small and of uncertain clinical relevance. Only one study[27] had a much lower score in the infusion group, which skewed the CI in the direction favoring the bolus group.

2. UA Outcomes

a. UA pH

Eight studies[4,20,23,24,26,27,37,38] assessed UA pH, a marker of neonatal acid–base balance. A small statistically significant difference in UA pH (MD −0.03) was observed favoring infusion, but this difference is clinically negligible, indicating similar neonatal acid–base balance between regimens [Supplementary Figure 6a]. All studies had virtually identical pH in the groups, which demonstrates that bolus and infusion doses provide comparable neonatal acid–base equilibrium.

b. UA paO2

Five studies[4,20,23,26,27] reported UA oxygen tension (paO_2), and the meta-analysis between infusion and bolus did not differ (MD −1.05, 95% CI [−2.83, 0.73]) [Supplementary Figure 6b]. The small number of available studies and wide CI limit the strength of the conclusions on this outcome. Overall, neither regimen was more effective with respect to neonatal oxygenation.

Publication bias assessment

Contour-enhanced funnel plots assessed publication bias for predelivery hypotension comparisons. The combined plot [Supplementary Figure 7a] showed right-sided clustering, suggesting possible bias toward bolus studies, though asymmetry outside significance contours ($P < 0.05$, 0.01, 0.001) may reflect methodological heterogeneity. Subgroup plots [Supplementary Figure 7b] for bolus versus variable-rate infusion and prophylactic bolus versus infusion were symmetrical, indicating low bias risk. Bolus versus fixed-rate infusion showed slight right skew, raising suspicion of selective bias, while therapeutic bolus versus infusion showed minimal asymmetry. Overall, asymmetry was limited and may

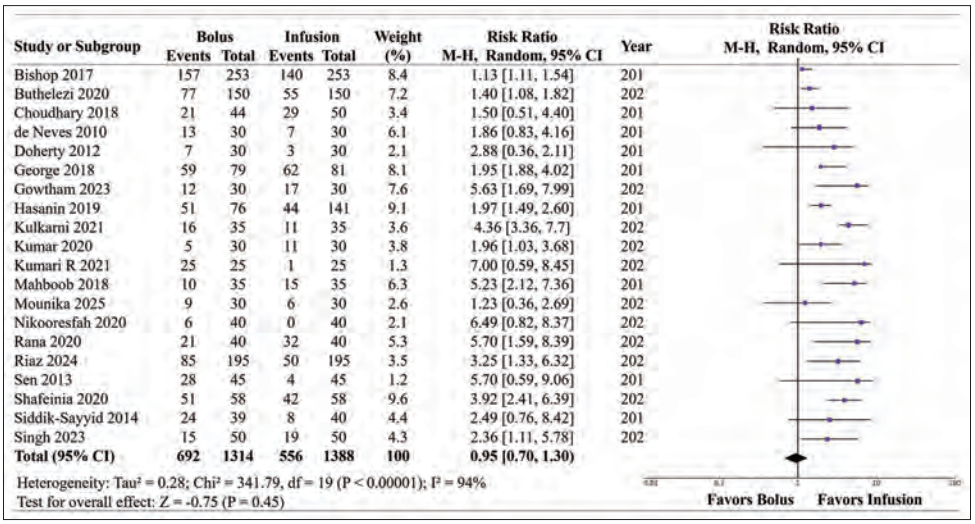

Figure 3: Forest Plots for the Incidence of Predelivery Hypotension with Phenylephrine Bolus and Infusion Regimens

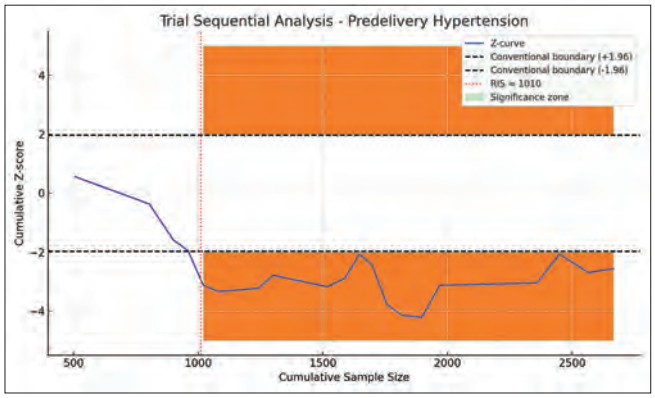

Figure 4: Trial Sequential Analysis (TSA) for predelivery hypotension. The cumulative Z-curve did not cross the trial monitoring boundary or reach the required information size (RIS), indicating that the overall evidence remains inconclusive. In contrast, TSA for the fixed-rate infusion subgroup (Supplementary Figure 8) crossed the benefit boundary, suggesting sufficient and stable evidence supporting the efficacy of fixed-rate infusion in preventing hypotension

reflect true heterogeneity or small-study effects. Additional outcome funnel plots are presented in the Supplementary Data. However, no quantitative tests (Egger's regression test) were performed, limiting the strength of conclusions regarding publication bias.

Trial sequential analysis

TSA indicated that the overall pooled evidence comparing infusion and bolus for predelivery hypotension remains inconclusive as the cumulative Z-curve did not cross significance or reach the required information size. In contrast, TSA for the prophylactic fixed-rate infusion subgroup crossed the boundary, providing sufficient evidence of benefit. For the therapeutic subgroup, the Z-curve remained within the nonsignificance zone, suggesting additional trials are needed to confirm [Figure 4]. These results should be explained clearly as TSA plots can be challenging for nonstatistical readers [Supplementary Figure 8].

Discussion/Comments

This systematic review and meta-analysis offers a current overview of the literature comparing phenylephrine bolus and infusion techniques for the prophylaxis and treatment of maternal hypotension during CD under neuraxial anesthesia. With 20 studies and more than 2742 parturients, the results provide important data on optimal VP control, maternal hemodynamic stability, and neonatal outcomes. The prophylaxis of maternal hypotension following neuraxial anesthesia remains one of the cornerstones in the safety of obstetric anesthesia.[36] Maternal hypotension can lead to nausea, vomiting, bradycardia, reduction of uteroplacental perfusion, and adverse neonatal outcomes.[37,38] However, the clinical practice of administering phenylephrine is very variable, with some centers using intermittent bolus dosing and others fixed or titrated infusions.[4] The current meta-analysis compares the efficacy and safety of these approaches to fill an important gap in comparative effectiveness.

Although fixed-rate infusion demonstrated benefit in subgroup analysis, the overall meta-analysis did not find a significant difference between infusion and bolus regimens. The advantage of fixed-rate infusion should thus be seen as a subgroup-specific finding rather than one of general superiority. In any case, these results are best interpreted with caution given the inconclusive pooled estimate and high heterogeneity. The apparent benefit of infusion might relate to more stable maintenance of blood pressure, but mechanistic explanations, such as superior physiological matching, remain speculative and were not directly tested in the included trials.[39,40] Subgroup analysis also confirmed this finding and reported that neither prophylactic nor therapeutic bolus provides advantages over fixed infusions, with some studies suggesting that continuous vasopressor infusion

Table 2: Summary of findings and GRADE evaluation for maternal and fetal outcomes between bolus and infusion

Outcomes	RR with infusion	RR with bolus	RR (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
Predelivery Hypotension	25%-42%	30%-55%	RR 1.40 [1.08, 1.82]	2742 (20 clinical trials)	[a]Moderate ⊕⊕⊕◯	Higher hypotension incidence in bolus group
Reactive Hypertension	5%-15%	3%-11%	RR 0.48 [0.30, 0.79]	1532 (8 clinical trials)	[b]Moderate ⊕⊕⊕◯	Lower reactive hypertension with bolus
Bradycardia	8%-15%	6%-13%	RR 0.91 [0.53, 1.54]	1553 (9 clinical trials)	[c]Very Low ⊕◯◯◯	No clear difference
Vomiting	3%-8%	5%-11%	RR 2.20 [0.87, 5.57]	1906 (14 clinical trials)	[d]Very Low ⊕◯◯◯	Uncertain increase in vomiting with bolus
Nausea	5%-10%	6%-12%	RR 0.95 [0.62, 1.47]	1157 (10 clinical trials)	[e]Low ⊕⊕◯◯	No significant difference in nausea
Apgar	8.5±1.5	8.9±1.2	MD 0.50 [0.19, 0.81]	1232 (11 clinical trials)	[f]Moderate ⊕⊕⊕◯	Slight improvement with bolus
UA pH	7.30±0.05	7.31±0.04	MD−0.03 [−0.04, −0.02]	643 (8 clinical trials)	[g]Moderate ⊕⊕⊕◯	Minimal clinical difference
UA paO2	19.2±4.0	18.5±5.0	MD−1.05 [−2.83, 0.73]	5 (540 clinical trials)	[h]Low ⊕⊕◯◯	Uncertain impact on neonatal oxygenation

GRADE Working Group evidence ratings. High certainty: we have a high degree of confidence that the actual effect is close to the effect estimate. Moderate certainty: we have a moderate level of confidence in the effect estimate; the genuine effect may differ significantly from the estimate, but it is likely to be close to it. Low certainty: we have little faith in the effect estimate because the actual effect might differ significantly from the estimate. Extremely low certainty: the actual effect is probably going to deviate significantly from the effect estimate; thus, we have very little faith in it. CI, confidence interval; RR, risk ratio. The relative effect of the intervention (and its 95% CI) and the anticipated risk in the comparison group serve as the basis for the risk in the intervention group (and its 95% CI). [a]5 studies (Bishop 2017, Buthelezi 2020, Choudhary 2018, Hasanin 2019, Kumari R 2021) out of 20 shows high risk [b]3 studies (Bishop 2017, Buthelezi 2020, Hasanin 2019) out of 8 shows high risk [c]3 studies (Bishop 2017, Buthelezi 2020, Hasanin 2019) out of 9 shows high risk [d]3 studies (Bishop 2017, Buthelezi 2020, Hasanin 2019) out of 14 shows high risk [e]3 studies (Bishop 2017, Buthelezi 2020, Hasanin 2019) out of 10 shows high risk [f]3 studies (Buthelezi 2020, Hasanin 2019, Kumari 2021) out of 11 shows high risk [g]2 studies (Choudhary 2018, Hasanin 2019) out of 8 shows high risk [h]2 studies Choudhary 2018, Hasanin 2019) out of 5 shows high risk

was associated with fewer hypotensive episodes, although mechanistic interpretations should be seen as hypothetical since most trials did not assess physiological parameters directly.[41,42] Moreover, therapeutic bolus delivery is reactive, thus leading to delays in treatment and subsequent hypotension compared to infusion. On the other hand, variable-rate infusions, while theoretically more flexible, did not appear noticeably superior to bolus delivery. This may be explained by either the difficulties of rapid titration of infusion rates against rapidly changing blood pressure or heterogeneity in study protocols.[28,32]

Reactive hypertension was significantly more common in the infusion group.[43,44] The lower incidence of reactive hypertension following bolus administration is also consistent with the findings of a higher overall dose with phenylephrine infusion compared with phenylephrine bolus.[8] Bradycardia occurred at similar frequencies in the bolus and infusion groups, although the individual studies did vary.[45,46] While not significantly different between groups in this review, the clinical approach should nevertheless remain individualized, particularly in parturients with reduced baseline HR or high spinal levels. These findings further highlight an important clinical trade-off. Therefore, whereas fixed-rate infusion may reduce the frequency of hypotensive episodes, it does so at the expense of increased reactive hypertension and possibly increased bradycardia. For most parturients, transient reactive hypertension is likely to be well tolerated; however, for patients with limited cardiac reserve or those sensitive to blood pressure fluctuations, this may pose additional risks. Clinicians should individualize the administration of phenylephrine based on maternal cardiovascular status, the degree of anticipated hemodynamic variability, and available monitoring capabilities. In resource-limited settings or in women at greater risk from hypertension or bradycardia, intermittent bolus dosing may offer a safer balance of efficacy to tolerability. On the other hand, fixed-rate infusion can be preferred in well-monitored environments aiming for tighter blood pressure control.

IONV is a distressing intraoperative complication of neuraxial anesthesia and can contribute to significant patient discomfort, anxiety, and dissatisfaction with the surgical experience.[47] The incidence of IONV during CD is significantly reduced by the administration of VPs.[48] In general, most of the analyses did not reach statistical significance for increased vomiting in the bolus group; however, data are too variable to rule out this effect. One possible mechanism for the increased vomiting in the bolus group is short hypotensive periods leading to vagal stimulation or ischemic gut. The delivery of phenylephrine by infusion may offer better hemodynamic control, with less potential for emesis.

The impact of postspinal hypotension on fetal physiology during CD is not well understood; however, experimental evidence suggests that prolonged decreases in uteroplacental blood flow can lead to fetal bradycardia and acidemia. Neonatal outcome, a factor of paramount concern in the assessment of VP strategies, was only slightly different in the compared regimens. The Apgar scores at 1 and 5 min, UA pH, and paO_2 were comparable, indicating that neither

administration strategy affected neonatal wellbeing. Although maternal hemodynamics were improved by fixed infusion, this did not lead to significant neonatal benefit, suggesting that transient hypotension, if appropriately managed, may not decrease fetal oxygenation or acid–base status. This point of evidence suggests that the choice of VP (ephedrine, with its higher transplacental transfer than phenylephrine) and the timing of administration may be better predictors of neonatal outcome.[50] While Apgar scores are indirectly influenced by maternal hemodynamics, they are not a direct or sensitive marker of maternal cardiovascular stability. Neonatal outcomes were statistically different in some measures but clinically equivalent. Although Apgar scores were slightly higher with bolus dosing and UA pH marginally higher with infusion, these differences were small, remained within normal physiological thresholds, and did not translate into clinical consequences such as need for resuscitation, NICU admission, or neonatal acidosis. Therefore, phenylephrine administration strategy did not meaningfully influence neonatal outcomes.

TSA was performed to determine whether the available evidence is sufficient to draw firm conclusions or if further studies are still needed. TSA applies monitoring boundaries similar to interim analyses in clinical trials and calculates the RIS, which is the minimum number of participants needed to make reliable conclusions while reducing random error and false positives. In our analysis, the cumulative Z-curve for the overall comparison between infusion and bolus did not cross the monitoring boundary or reach the RIS, indicating that the current evidence is inconclusive and additional trials are required. However, in the subgroup of fixed-rate prophylactic infusion, the Z-curve crossed the benefit boundary, demonstrating that the evidence for reduced predelivery hypotension in this subgroup is statistically robust and unlikely to change with further studies. In contrast, TSA for therapeutic bolus versus infusion remained inconclusive. Therefore, TSA confirms that while fixed-rate infusion may be effective in preventing hypotension, the overall superiority of infusion over bolus cannot be established with current data.

This study has several limitations. First, substantial heterogeneity was observed for certain outcomes, likely attributable to variability in phenylephrine dosing regimens, coadministration of intravenous fluids, spinal anesthetic protocols, and inconsistently defined outcome measures such as hypotension, bradycardia, and nausea. Second, many trials lacked adequate blinding or used subjective outcome assessments, especially for emetogenic events such as nausea and vomiting, increasing the risk of performance and detection bias. Although subgroup analyses were conducted to account for differences in infusion protocols and bolus timing, residual interstudy heterogeneity could not be fully eliminated, and therefore, the findings particularly regarding the relative performance of fixed versus variable-rate infusions should be interpreted with caution. The high statistical heterogeneity observed in the primary outcome (I^2 =94%) is likely attributable to multiple clinical and methodological differences across studies. These include variability in phenylephrine dose and infusion rates (e.g., μg/min versus μg/kg/min), timing of administration (prophylactic vs therapeutic), coadministration of fluid preloading or coloading strategies, spinal anesthetic doses, and inconsistent definitions of hypotension (ranging from <90 mmHg to <80% of baseline SBP). Furthermore, outcome measurement timepoints were not standardized across trials. Although we attempted subgroup analyses to minimize variability, there was the reporting of key covariates such as total phenylephrine dose, baseline maternal blood pressure, fluid volume administered, and spinal block height that was inconsistent across studies. For this reason, meta-regression could not be performed, preventing formal statistical assessment of potential heterogeneity sources. Consequently, the findings should be interpreted cautiously, particularly when comparing fixed- versus variable-rate infusion strategies. Finally, the absence of a universal definition of maternal hypotension across studies complicates direct comparisons. Consensus on standard outcome definitions is required for future meta-analyses to pool the results in a more uniform and clinically applicable manner. Second, the search strategy was restricted to English-language studies only, potentially introducing language bias and excluding relevant data published in other languages. Most of the included studies enrolled low-risk parturients and excluded women with pre-eclampsia, cardiac disease, or any other comorbidities. Thus, the results may not be widely generalizable to high-risk obstetric populations in whom the hemodynamic responses and vasopressor requirements can be quite different.

Despite these limitations, evidence from this study offers practical recommendations. Based on current evidence, prophylactic fixed-rate infusion appears to offer the most consistent hemodynamic control, but its advantage is supported primarily in low-risk parturients and may not extend to all clinical contexts. The overall pooled analysis was inconclusive, and therapeutic bolus regimens remain insufficiently studied. Neonatal outcomes were comparable between strategies, and the small statistical differences observed (Apgar score MD 0.5) are unlikely to be clinically meaningful. In well-resourced settings with continuous monitoring, fixed-rate infusion can be preferred for prophylaxis. However, in resource-limited settings or in women with baseline bradycardia or cardiovascular sensitivity, bolus administration remains a reasonable and safe alternative.[49] Bolus is still an appropriate alternative, especially in resource-constrained settings or in patients at

increased risk of hypertension or bradycardia.[27] It is also important to contextualize our findings along with related evidence to evaluate hybrid administration strategies. While our meta-analysis focused on direct comparisons between phenylephrine bolus and infusion regimens, it is noteworthy that other administration strategies have been studied. Siddik-Sayyid *et al.* (2014)[27] conducted an RCT comparing prophylactic variable-rate phenylephrine infusion plus rescue bolus as required with a rescue bolus-only approach. Their findings indicated that the infusion regimen plus rescue bolus was superior to bolus administration in avoiding PSH, nausea, and vomiting, and in reducing the need for further clinical interventions. These results were subsequently highlighted in the international consensus statement by Kinsella *et al.* (2017),[50] where the bolus-only regimen was referred to as "reactive treatment" and prophylactic infusion regimens in elective CD were advocated. Although Siddik-Sayyid *et al.* (2014) demonstrated the additive benefit of a combination strategy, variable-rate phenylephrine infusion plus rescue boluses, over bolus-only management, this composite approach was beyond the scope of our study, which compared infusion and bolus as standalone (monotherapy) regimens. Further research is needed to evaluate whether combination strategies provide meaningful clinical advantages over monotherapy, particularly in high-risk subgroups.

Conclusion

This systematic review and meta-analysis indicates that prophylactic fixed-rate phenylephrine infusion may reduce the incidence of predelivery hypotension compared with bolus dosing, although the overall pooled evidence remains inconclusive due to substantial heterogeneity. TSA supports fixed-rate infusion only for prophylactic use, while evidence for therapeutic bolus regimens is underpowered and warrants further research. The observed increase in reactive hypertension with infusion underscores the need to balance hypotension prevention against potential adverse hemodynamic effects. Neonatal outcomes, including Apgar scores and umbilical blood gases, showed minor statistical differences but remained within normal ranges and were clinically indistinguishable between infusion and bolus regimens. While fixed-rate phenylephrine infusion demonstrated reduced predelivery hypotension in subgroup analyses, the overall pooled evidence did not show a significant difference between infusion and bolus regimens. TSA confirmed this uncertainty. Infusion was also associated with a higher risk of reactive hypertension. Therefore, infusion should be considered a potentially beneficial, but not definitively superior, strategy. Maternal hemodynamic goals and resource availability should guide clinical decisions.

Ethics statement

Not required because all analyses were based on previously published studies.

Data availability

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

AI use statement

Portions of the manuscript, including text formatting, grammar editing, and figure labeling, were supported by the use of generative AI tools (e.g., ChatGPT, OpenAI), under the supervision and final approval of the authors. No AI tools were used for data extraction, analysis, or interpretation.

Author contributions

Arya Babul – Literature search, data acquisition, data extraction, drafting of manuscript.

Sohi Ashraf – Concept, study design, interpretation of results, manuscript review.

Jyoti Desai – Data analysis, interpretation of results, manuscript editing.

Leanne Free – Preparation of tables/figures, manuscript editing.

Momina Hussain – Literature search, risk of bias assessment, statistical analysis, data synthesis, manuscript preparation.

Najib Babul – Concept, study design, supervision, critical revision for intellectual content, guarantor of the work.

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Conflicts of interest

There are no conflicts of interest.

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Additional Supplementary Data

Contour-enhanced funnel plots for assessing publication bias of postdelivery hypotension, reactive hypertension, bradycardia, intraoperative nausea and vomiting (IONV), and neonatal outcomes.

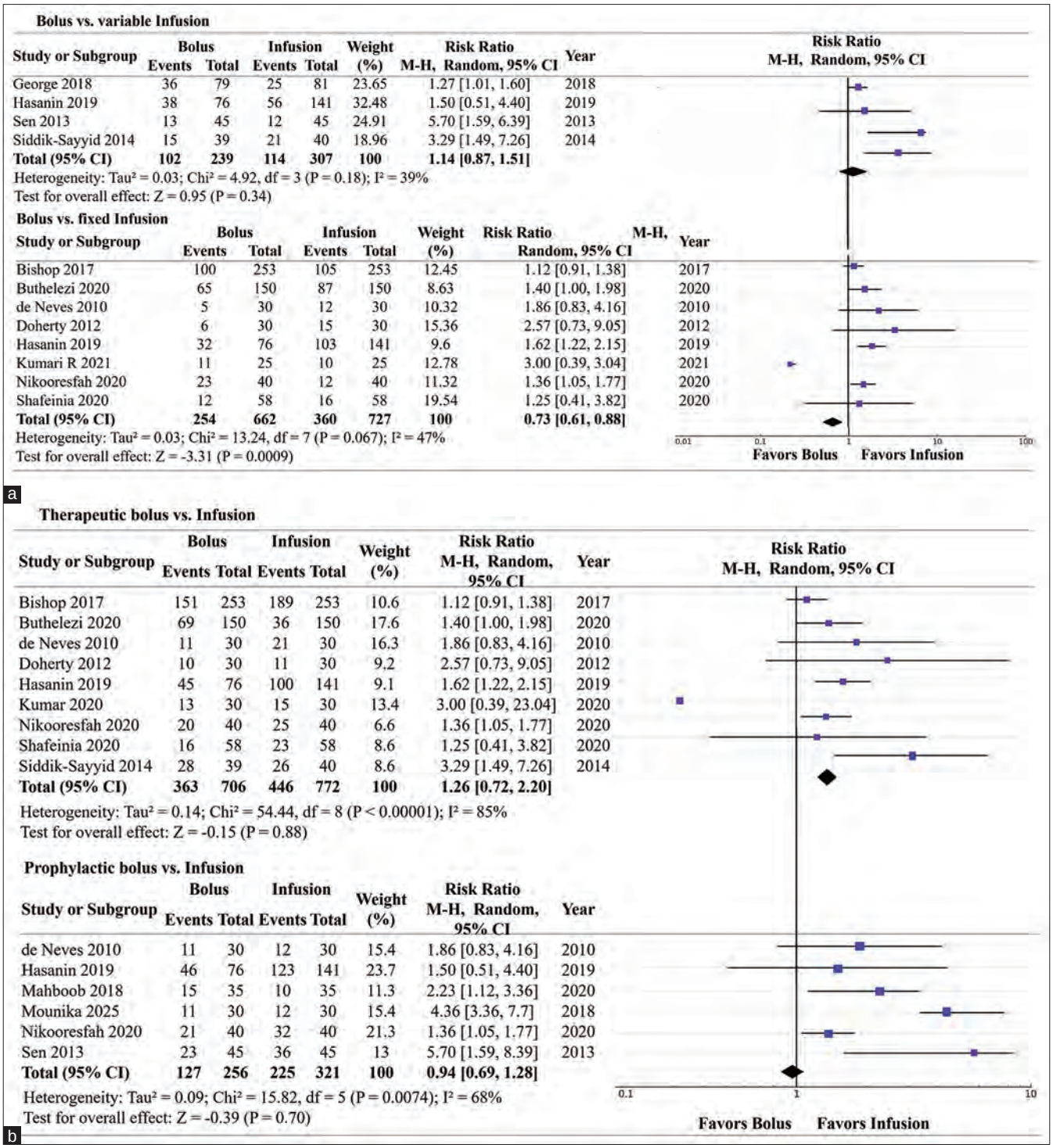
Appendices

Appendix I: PRSIMA Checklist

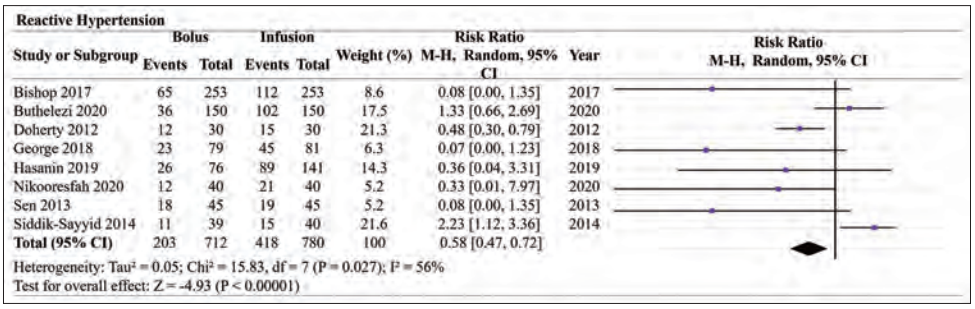
Section and Topic	Item #	Checklist item	Reported on page #
TITLE	1	Identify the report as a systematic review.	1
ABSTRACT	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION	3	Describe the rationale for the review in the context of existing knowledge.	2 & 3
INTRODUCTION	4	Provide an explicit statement of the objective (s) or question (s) the review addresses.	2 & 3
METHODS	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3 & 4
METHODS	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3 & 4
METHODS	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3 & 4
METHODS	8	Specify the methods used to decide whether a study met the inclusion criteria of the review.	3 & 4
METHODS	9	Specify the methods used to collect data from reports.	3 & 4
METHODS	10a	List and define all outcomes for which data were sought.	5
METHODS	10b	List and define all other variables for which data were sought.	5
METHODS	11	Specify the methods used to assess risk of bias.	5
METHODS	12	Specify for each outcome the effect measure (s).	5
METHODS	13a	Describe the processes used to decide which studies were eligible for each synthesis.	5 & 6
METHODS	13b	Describe any methods required to prepare the data.	5 & 6
METHODS	13c	Describe any methods used to tabulate or visually display results.	5 & 6
METHODS	13d	Describe any methods used to synthesize results.	5 & 6
METHODS	13e	Describe any methods used to explore possible causes of heterogeneity.	5 & 6
METHODS	13f	Describe any sensitivity analyses conducted.	5 & 6
METHODS	14	Describe any methods used to assess risk of bias due to missing results.	7
METHODS	15	Describe any methods used to assess certainty.	7
RESULTS	16a	Describe the results of the search and selection process.	8, Figure 1
RESULTS	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded.	8
RESULTS	17	Cite each included study and present its characteristics.	9 & 10, Table 1
RESULTS	18	Present assessments of risk of bias for each included study.	10, Figure 2
RESULTS	19	For all outcomes, present, for each study: (a) summary statistics. (b) an effect estimate.	11 & 13, Figures 3 & 6
RESULTS	20a	For each synthesis, briefly summarize the characteristics and risk of bias.	13 & 14
RESULTS	20b	Present results of all statistical syntheses conducted.	13 & 14
RESULTS	20c	Present results of all investigations of possible causes of heterogeneity.	13 & 14
RESULTS	20d	Present results of all sensitivity analyses.	13 & 14
RESULTS	21	Present assessments of risk of bias due to missing results.	14, Figure 7
RESULTS	22	Present assessments of certainty in the body of evidence.	14, Table 2
DISCUSSION	23a	Provide a general interpretation of the results.	15 & 17
DISCUSSION	23b	Discuss any limitations of the evidence.	15 & 17
DISCUSSION	23c	Discuss any limitations of the review processes.	15 & 17
DISCUSSION	23d	Discuss implications of the results for practice, policy, and future research.	15 & 17
OTHER INFORMATION	24a	Provide registration information for the review.	3
OTHER INFORMATION	24b	Indicate where the review protocol can be accessed.	3
OTHER INFORMATION	24c	Describe and explain any amendments to information provided.	Not applicable
OTHER INFORMATION	25	Describe sources of financial or non-financial support.	1
OTHER INFORMATION	26	Declare any competing interests of review authors.	1
OTHER INFORMATION	27	Report which of the following are publicly available and where.	1

Appendix II: Summary of study selection process for inclusion in the systematic review

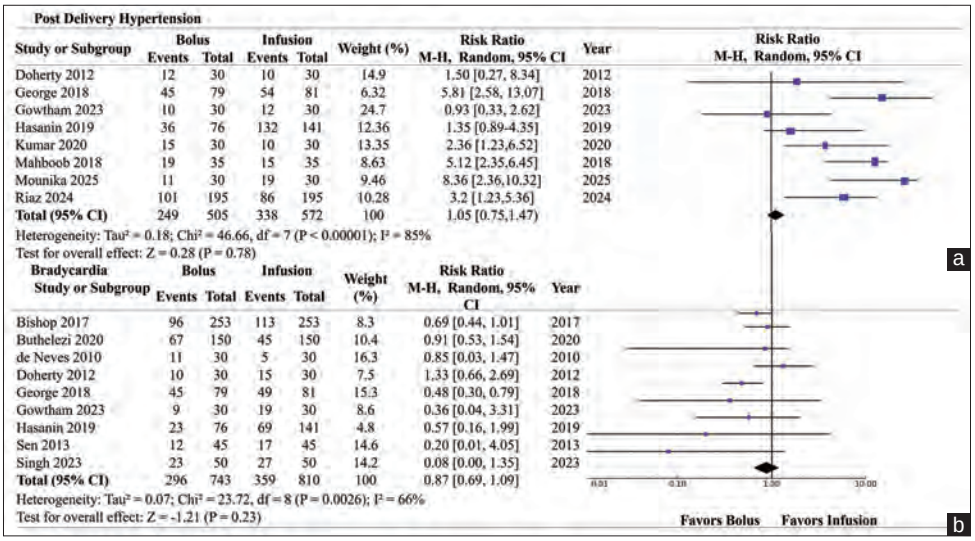
Source	Search String
Pubmed	(("Phenylephrine"[Mesh] OR phenylephrine[tiab]) AND ("Cesarean Section"[Mesh] OR cesarean[tiab] OR caesarean[tiab] OR "c-section"[tiab]) AND ("Hypotension"[Mesh] OR hypotension[tiab] OR "blood pressure"[tiab]) AND (bolus[tiab] OR infusion[tiab] OR "intravenous administration"[tiab] OR IV[tiab]) AND ("Spinal Anesthesia"[Mesh] OR "spinal anesthesia"[tiab] OR "combined spinal epidural"[tiab] OR "neuraxial anesthesia"[tiab])) AND ("Randomized Controlled Trial"[pt] OR "controlled clinical trial"[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trial"[tiab])
Cochrane Library	phenylephrine AND (cesarean OR caesarean OR "c-section") AND (hypotension OR "blood pressure") AND (bolus OR infusion OR "intravenous administration" OR IV) AND ("spinal anesthesia" OR "combined spinal epidural" OR "neuraxial anesthesia") AND (randomized OR trial OR RCT)
Embase	('vasopressor agent'/exp OR vasopressor*:ab, ti OR phenylephrine: ab, ti OR norepinephrine: ab, ti OR ephedrine: ab, ti) AND ('hypotension'/exp OR hypotension: ab, ti OR 'low blood pressure':ab, ti) AND ('cesarean section'/exp OR 'cesarean delivery':ab, ti OR 'caesarean section':ab, ti) AND ('spinal anesthesia'/exp OR 'spinal anesthesia':ab, ti OR 'subarachnoid block':ab, ti) AND (treatment: ab, ti OR therapeutic: ab, ti) AND ([randomized controlled trial]/lim OR [clinical trial]/lim)
Science Direct	phenylephrine AND cesarean AND hypotension AND (bolus OR infusion) AND "spinal anesthesia" AND randomized



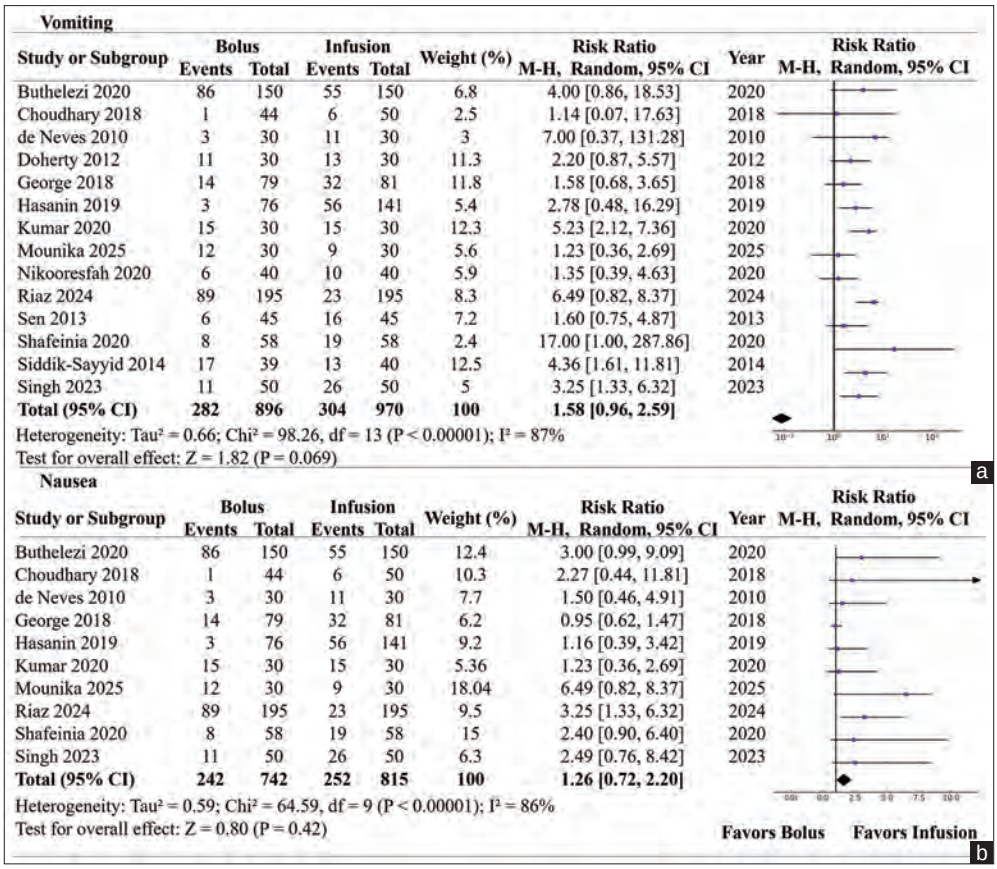
Supplementary Figure 1: Forest Plots for the Subgroup comparison of Incidence of Predelivery Hypotension with Phenylephrine Bolus and Infusion Regimens. (a) Subgroup comparison between bolus and variable-rate infusion (above) and fixed-rate infusion (below). (b) Subgroup comparison between therapeutic bolus (above) and prophylactic bolus (below) and infusion regimens



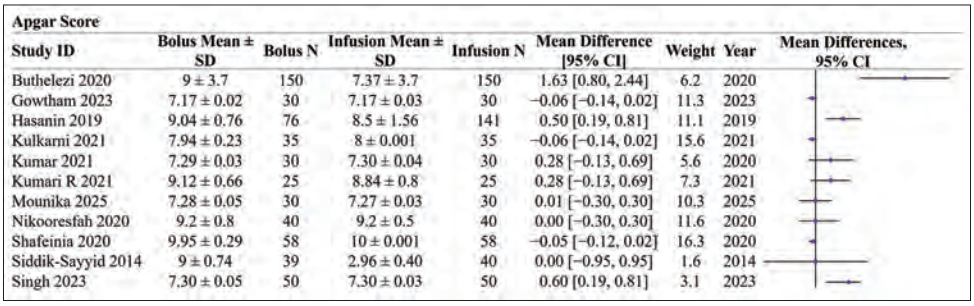
Supplementary Figure 2: Forest Plots Contrasting Phenylephrine Bolus vs Infusion Regimens on Reactive hypertension Maternal Hemodynamic Outcomes



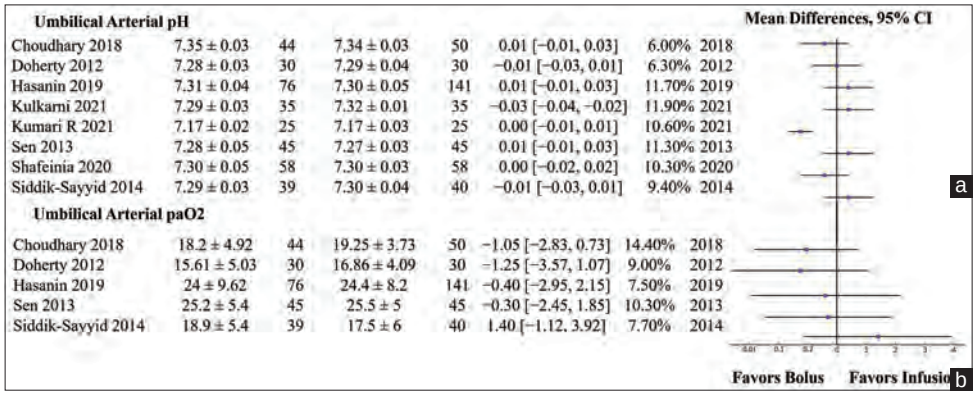
Supplementary Figure 3: Forest Plots Contrasting Phenylephrine Bolus vs Infusion Regimens on Secondary Maternal Hemodynamic Outcomes. (a) Hypotension following delivery: no significant difference. (b) Bradycardia: no significant difference between bolus and infusion



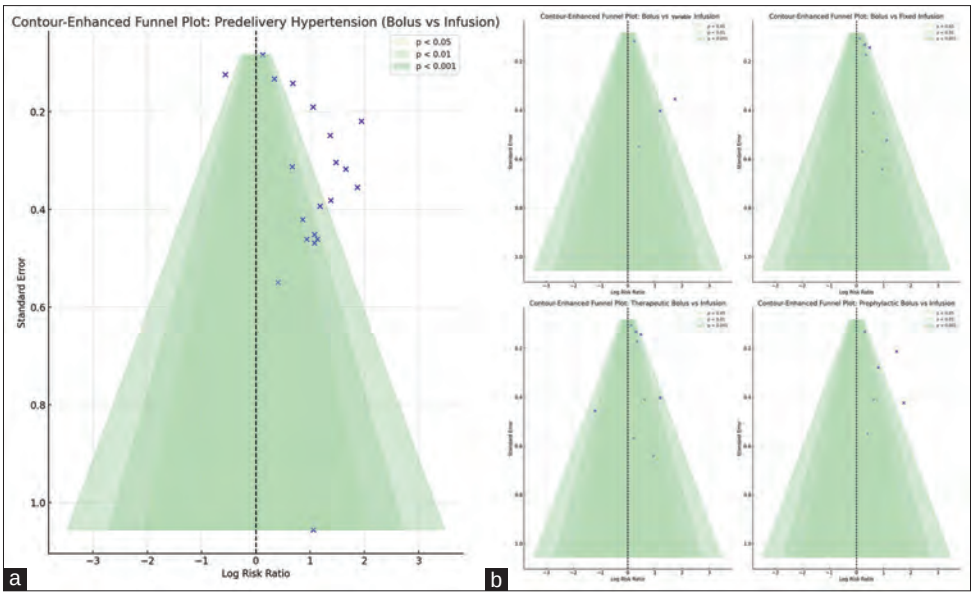
Supplementary Figure 4: Forest Plots Comparing Phenylephrine Infusion and Bolus Regimens for IONV During CD. (a) Vomiting: trend toward increased incidence with bolus, not significant. (b) Nausea: no group difference



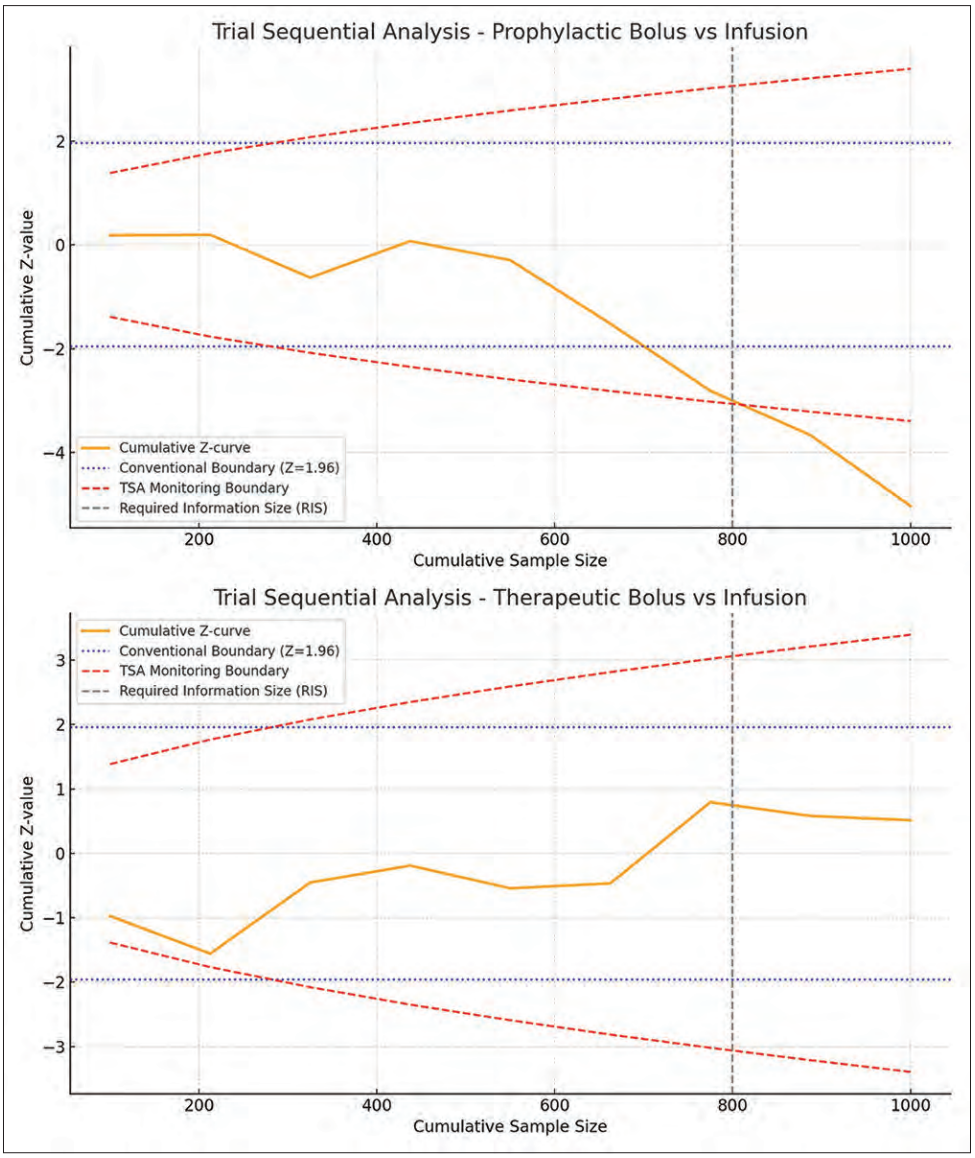
Supplementary Figure 5: Forest Plots of Phenylephrine Infusion vs Bolus Regimens on Neonatal Outcomes (Apgar score) after CD



Supplementary Figure 6: Forest Plots of Phenylephrine Infusion vs Bolus Regimens on Neonatal Outcomes after CD. (a) UA pH: marginally higher with infusion, but not clinically meaningful. (b) UA paO_2: no significant difference



Supplementary Figure 7: Contour-Improved Funnel Plots Assessing Publication Bias for Predelivery Hypotension: (a) Total bolus vs. infusion contrast; (b) Subgroup analyses of bolus vs. variable-rate infusion (upper left), fixed-rate infusion (upper right), therapeutic bolus (lower left), and prophylactic bolus (lower right). Hatched areas indicate significance levels ($P < 0.05$, 0.01, 0.001)



Supplementary Figure 8: Trial Sequential Analysis for Predelivery Hypotension: Subgroup TSA of prophylactic bolus vs. infusion (top) shows conclusive evidence; therapeutic bolus vs. infusion (bottom) remains inconclusive