Open Journal of Anesthesiology, 2025, 15(12), 370-388
https://www.scirp.org/journal/ojanes
ISSN Online: 2164-5558
ISSN Print: 2164-5531

Comparison of the Efficacy of Low-Concentration Norepinephrine and Ephedrine in the Management of Post-Spinal Hypotension for Cesarean Section: A Prospective Analytical Study

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How to cite this paper: Raja, A., Ahmad, Y., Mandour, Y., Joutey, O.T., Thyifa, M., Afif, A., El Youssoufi, S. and Salmi, S. (2025) Comparison of the Efficacy of Low-Concentration Norepinephrine and Ephedrine in the Management of Post-Spinal Hypotension for Cesarean Section: A Prospective Analytical Study. *Open Journal of Anesthesiology*, **15**, 370-388.
https://doi.org/10.4236/ojanes.2025.1512026

Received: September 13, 2025
Accepted: December 23, 2025
Published: December 26, 2025

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Abstract

Background: Post-spinal hypotension remains the most formidable complication of spinal anesthesia for cesarean delivery, occurring in 70% - 80% of cases and compromising maternal-fetal safety. While ephedrine has long dominated therapeutic management, growing concerns about fetal acidosis have directed research toward safer alternatives. Norepinephrine emerges as a promising candidate with balanced pharmacological properties. This study compares three approaches: bolus ephedrine, bolus norepinephrine, and prophylactic continuous norepinephrine infusion. **Methods:** Prospective analytical study including 170 parturients undergoing cesarean delivery under spinal anesthesia at University Hospital Mother and Child Harouchi, Ibn Rochd, Hassan II University (February to June 2025). Computer-generated block randomization with sealed envelope allocation concealment into three balanced groups: Group I (ephedrine 3 - 6 mg bolus, n = 57), Group II (norepinephrine 8 - 16 µg bolus, n = 56), Group III (prophylactic continuous norepinephrine infusion 5 µg/kg, n = 57). Sample size calculated a priori for 80% power to detect a 20% difference in efficacy with $\alpha = 0.05$. Baseline blood pressure is defined as the mean of three measurements after a 10-minute rest. Hemodynamic evaluation at four operative time points. Primary endpoint: hypotension correction efficacy (restoration of SBP > 80% baseline values within 5 minutes of first vasopressor administration). Secondary endpoints: hemodynamic stability, maternal tolerance, neonatal adaptation. **Results:** Baseline hemodynamic parameters were equivalent among groups ($p > 0.05$), confirming successful randomization. Highly significant he-

modynamic differences between groups during intervention. Group II: fastest blood pressure recovery (SBP 126.2 mmHg ± 1.3 mmHg at T2 vs 80.5 mmHg ± 3.8 mmHg Group I, $p < 0.001$), optimal cardiac stability (HR 87.5 bpm ± 4.7 bpm vs 133.7 bpm ± 6.3 bpm Group I, $p < 0.001$). Group III: effective prevention of severe hypotension (MAP maintained at 82.9 mmHg ± 10.6 mmHg at T1) but inter-individual variability requiring supplemental ephedrine (20% of cases). Therapeutic efficacy: 94% (Group III), 89% (Group II), 68% (Group I), $p < 0.001$. Comparable Apgar scores, superior maternal satisfaction with norepinephrine ($p < 0.001$). No catecholamine-related arrhythmias are observed during continuous cardiac monitoring. **Conclusion:** Norepinephrine demonstrates clear superiority over ephedrine in managing post-spinal hypotension. Bolus administration offers the best efficacy-safety ratio with rapid hemodynamic recovery and optimal tolerance. Prophylactic continuous infusion represents a promising therapeutic innovation for preventing severe hypotension, redefining management paradigms in obstetric anesthesia.

Keywords

Spinal Anesthesia, Hypotension, Cesarean Section, Norepinephrine, Ephedrine, Hemodynamics, Obstetric Anesthesia

1. Introduction

1.1. History and Evolution of Spinal Anesthesia

Spinal anesthesia, born in the late 19th century with August Bier's pioneering work in 1898, represents a major innovation in anesthesiology [1]. The evolution of local anesthetics (procaine in 1905, lidocaine in 1943, bupivacaine in the 1960s) and the introduction of "pencil-point" needles in the 1980s facilitated its widespread adoption [2]-[4]. Today, spinal anesthesia represents the technique of choice for more than 95% of elective cesarean sections [5].

1.2. Hypotension: Major Complication in Pregnant Women

Post-spinal hypotension constitutes the most frequent complication in obstetrics, occurring in 70% - 80% of cases compared to 20% - 30% in general surgery [6]. This particular vulnerability of pregnant women results from specific anatomophysiological modifications: aortocaval compression by the gravid uterus, reducing venous return by 30% - 50%, increased sensitivity to local anesthetics, and pregnancy-related cardiovascular adaptations [7]-[9].

Maternal hypotension compromises uteroplacental perfusion, exposing the fetus to hypoxia and acidosis [10]. It manifests clinically through nausea, vomiting, and in severe cases, maternal loss of consciousness [11].

1.3. Evolution of Vasopressors

Ephedrine has long dominated management due to its mixed α and β-adrenergic

action [12]. However, the landmark study by Cooper *et al.* (2002) demonstrated its responsibility in fetal acidosis, initiating a paradigmatic shift [13]. Phenylephrine then emerged as a safer alternative, but its pure vasoconstrictor action can induce reflex bradycardia [14].

Norepinephrine, an endogenous catecholamine combining predominant $\alpha 1$-adrenergic activity with moderate $\beta 1$-adrenergic effect, presents a theoretically optimal profile [15]. Recent studies confirm its efficacy with better hemodynamic stability [16] [17]. A 2024 systematic review and network meta-analysis by Zhang *et al.* demonstrated norepinephrine's superior hemodynamic profile compared to both ephedrine and phenylephrine in obstetric populations, with improved maternal outcomes and equivalent neonatal safety [18].

1.4. Study Justification

Despite favorable evidence, questions persist regarding the optimal administration modality of norepinephrine: curative boluses versus prophylactic continuous infusion. Direct comparative data with ephedrine is conspicuously sparse. Our study aims to fill these gaps by comparing three strategies: bolus ephedrine, bolus norepinephrine, and continuous norepinephrine infusion, to determine the optimal therapeutic approach.

2. Materials and Methods

2.1. Study Design and Ethical Considerations

Prospective analytical study conducted from February to June 2025 at the Department of Maternity Intensive Care, University Hospital Mother and Child Harouchi, Ibn Rochd, Hassan II University, Casablanca. The protocol was approved by the institutional ethics committee with informed consent from all participants (Reference: EC-2025-02-15).

Inclusion criteria: Adult patients (≥18 years), singleton pregnancy at term (≥37 weeks), ASA I-II, elective cesarean section under spinal anesthesia, post-spinal hypotension (SBP < 90 mmHg or decrease >30% from baseline values).

Exclusion criteria: Cardiovascular pathology, contraindication to spinal anesthesia, emergency cesarean section, vasopressor allergy, refusal to participate, multiple pregnancy, preeclampsia.

2.2. Randomization Sequence Generation and Allocation Concealment

Randomization sequence generation: Computer-generated randomization sequence using permuted blocks of varying sizes (3, 6, 9) created by an independent statistician using R software (version 4.3.0). The randomization list was stratified by maternal age (<30 vs ≥30 years) to ensure balanced allocation across age groups and minimize potential confounding effects.

Allocation concealment: Allocation concealment achieved through sequentially numbered, opaque, sealed envelopes prepared by research personnel not involved

in patient recruitment or clinical care. Envelopes were stored in a locked cabinet and opened only after patient enrollment, informed consent, and completion of baseline measurements by the attending anesthesiologist. This process ensured that neither the investigators nor the clinical staff could predict treatment assignment.

2.3. Sample Size Calculation

A priori power calculation: Based on pilot data from our institution showing 70% efficacy with ephedrine versus 90% with norepinephrine for hypotension correction, with $\alpha = 0.05$ and $\beta = 0.20$ (80% power), the calculated sample size was 51 patients per group using Fisher's exact test. Accounting for a 10% dropout rate and potential protocol violations, 57 patients were recruited per group, totaling 170 patients. This sample size provides adequate power to detect a clinically meaningful difference of 20% between groups for the primary endpoint.

2.4. Anesthetic Protocol

Standardized spinal anesthesia in sitting position (L3-L4, L4-L5, or L5-S1) with 25 25-G pencil-point needle (Whitacre, BD Medical). Solution: hyperbaric bupivacaine 0.5% (10 - 12.5 mg) + fentanyl 25 µg. Positioning in the supine position with 15˚ left lateral tilt using a standardized wedge. Standard monitoring: ECG, SpO_2, NIBP every 2 minutes, continuous cardiac rhythm monitoring for arrhythmia detection throughout the procedure.

Baseline blood pressure definition: Baseline blood pressure was defined as the mean of three consecutive measurements taken 5 minutes apart in the pre-operative holding area, with the patient in supine position with left lateral tilt, after 10 minutes of rest. All measurements were performed using the same automated oscillometric device (Philips IntelliVue MP70) with an appropriate cuff size, calibrated daily according to manufacturer specifications.

2.5. Therapeutic Protocols

Group I (n = 57): Ephedrine 5 mg/mL (Aguettant, France), bolus 3 - 6 mg IV every 2 minutes until SBP restoration (maximum cumulative dose 30 mg).

Group II (n = 56): Norepinephrine 16 µg/mL (diluted from 1 mg/mL ampoules, Aguettant, France), bolus 8 - 16 µg IV according to hemodynamic response, repeated every 2 minutes as needed.

Group III (n = 57): Norepinephrine 16 µg/mL in prophylactic continuous infusion via syringe pump (initial rate 8 mL/h ≈ 5 µg/kg/h), started immediately after spinal injection, adjusted to maintain SBP ≥ 90% of baseline values.

2.6. Study Parameters and Definitions

Hemodynamic variables: HR, SBP, DBP, MAP recorded at times T0 (pre-spinal baseline), T1 (5 minutes post-spinal), T2 (fetal delivery), T3 (skin closure).

Neonatal variables: Apgar scores (1, 5, 10 minutes), birth weight, umbilical cord

blood gas analysis, pediatric evaluation.

Primary endpoint: Hypotension correction efficacy, defined as restoration of SBP > 80% baseline values within 5 minutes of the first vasopressor administration. The 5-minute window starts from the moment of first drug injection (time zero = first vasopressor bolus administration).

Secondary endpoints: Hemodynamic stability (coefficient of variation of SBP), maternal tolerance (nausea, vomiting, satisfaction score), neonatal adaptation (Apgar scores, cord blood pH), and total vasopressor consumption.

Safety monitoring: Continuous cardiac rhythm monitoring throughout the procedure using 3-lead ECG for detection of arrhythmias (atrial fibrillation, ventricular ectopy, bradycardia < 50 bpm, tachycardia > 120 bpm), hypertensive episodes (SBP >160 mmHg), and clinical assessment of other catecholamine-related adverse events (tremor, anxiety, peripheral vasoconstriction).

2.7. Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY). Quantitative variables expressed as mean ± standard deviation or median [interquartile range] according to distribution. Normality was assessed using the Shapiro-Wilk test. Comparisons between groups were performed using one-way ANOVA with post-hoc Tukey tests for normally distributed variables, Kruskal-Wallis test with Dunn's post-hoc for non-parametric data, and Chi-square or Fisher's exact test for categorical variables. The significance threshold set at $p < 0.05$. Intention-to-treat analysis performed for all randomized patients.

3. Results

3.1. Baseline Characteristics and Hemodynamic Equivalence

Demographic analysis reveals satisfactory homogeneity between the three therapeutic cohorts. Mean maternal age was 28.4 years ± 5.2 years (Group I), 29.1 years ± 4.8 years (Group II), and 28.7 years ± 5.1 years (Group III), with no statistically significant difference (p = 0.742). Pre-pregnancy body mass index remained comparable between groups (24.8 kg/m^2 ± 3.1 kg/m^2 vs 25.2 kg/m^2 ± 2.9 kg/m^2 vs 24.6 kg/m^2 ± 3.3 kg/m^2, p = 0.658).

Maternal parity showed no inter-group disparity, with a proportion of primiparous women of 52.6% (Group I), 51.8% (Group II), and 54.4% (Group III). Gestational age at the time of surgical intervention was homogeneous: 38.9 weeks ± 1.2 weeks of amenorrhea for the entire study population (**Table 1**).

Table 1. Baseline hemodynamic parameters at T0 (pre-spinal).

Parameter	Group I (Ephedrine) n = 57	Group II (Norepinephrine Bolus) n = 56	Group III (Norepinephrine Infusion) n = 57	p-value
Heart Rate (bpm)	78.2 ± 2.1	79.1 ± 2.3	77.8 ± 2.0	0.052
Systolic BP (mmHg)	128.5 ± 4.2	127.8 ± 3.9	129.2 ± 4.1	0.341

Continued

Diastolic BP (mmHg)	78.3 ± 3.1	77.9 ± 2.8	78.7 ± 3.0	0.456
Mean Arterial Pressure (mmHg)	95.2 ± 3.1	94.8 ± 2.8	96.1 ± 3.0	0.287

Data expressed as mean ± standard deviation. BP: Blood Pressure. No significant differences between groups ($p > 0.05$), confirming successful randomization and hemodynamic equivalence at baseline.

3.2. Perioperative Hemodynamic Parameters

3.2.1. Heart Rate Evolution

Chronological analysis of heart rate reveals diametrically opposed evolutionary profiles according to the vasopressor strategy employed. Group I (ephedrine) presents progressive and sustained tachycardia, with heart rate peaking at 133.7 beats ± 6.3 beats per minute at time T2 (fetal delivery), representing a 71% increase from baseline values ($p < 0.001$) (**Figure 1**).

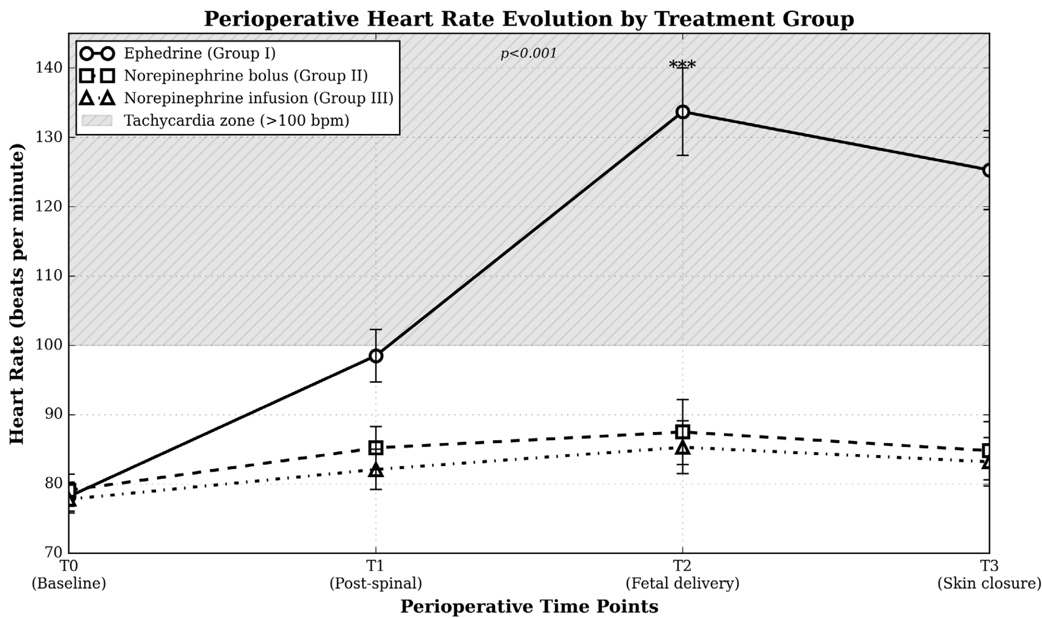

Figure 1. Perioperative heart rate evolution by therapeutic group. Curves represent means ± standard error. The hatched zone delimits tachycardia (>100 bpm). Asterisks indicate statistical significance (***$p < 0.001$) between groups at times T1 and T2.

Conversely, Groups II and III (norepinephrine) maintain remarkable chronotropic stability. Group II displays a heart rate of 87.5 bpm ± 4.7 bpm at T2, while Group III maintains a rate of 85.3 bpm ± 3.8 bpm, representing variations of less than 10% from reference values. This inter-group difference reaches major statistical significance ($p < 0.001$) at times T1, T2, and T3.

3.2.2. Systolic Blood Pressure Dynamics

Evolution of systolic blood pressure constitutes the principal discriminating parameter of therapeutic efficacy. Group I presents profound and prolonged hypotension, with systolic pressure dropping to 80.5 mmHg ± 3.8 mmHg at time T1, repre-

senting a 37% decrease from pre-anesthetic values. Blood pressure recovery proves slow and incomplete, reaching only 95.2 mmHg ± 4.5 mmHg at T2 (Figure 2).

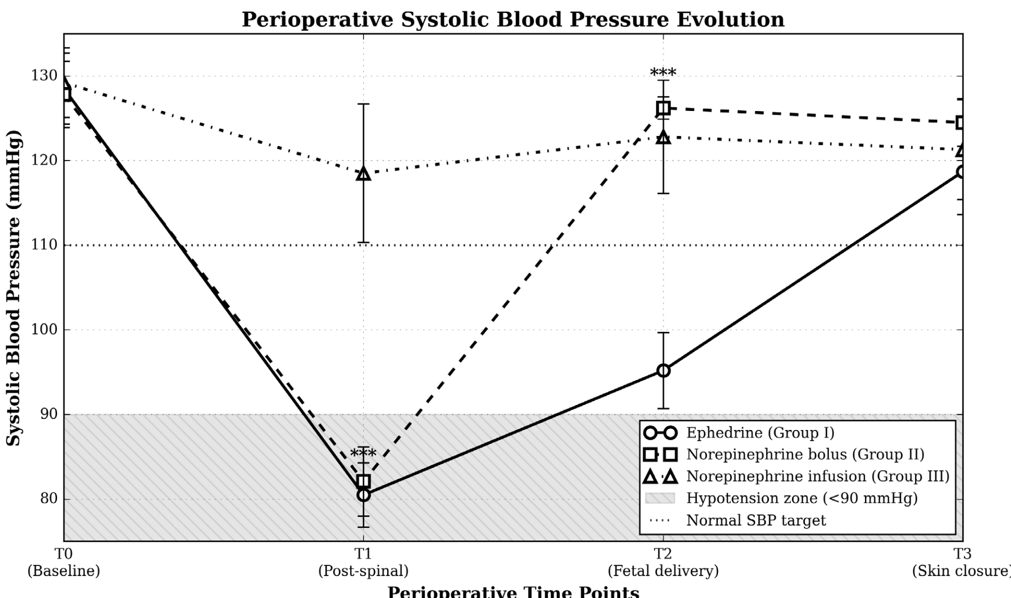

Figure 2. Perioperative systolic blood pressure evolution. Curves represent means ± standard error. The hatched zone delimits hypotension (<90 mmHg). The dotted line indicates the normal blood pressure target. Statistical annotations show significant differences between groups.

Group II demonstrates exceptional blood pressure recovery capacity, with rapid restoration to 126.2 mmHg ± 1.3 mmHg by T2, even exceeding baseline values. This therapeutic performance translates to a highly significant difference compared to Group I ($p < 0.001$).

Group III, benefiting from the prophylactic approach, maintains a systolic pressure of 118.5 mmHg ± 8.2 mmHg at T1, thus limiting the amplitude of the initial blood pressure drop. This preventive strategy proves statistically superior to both other approaches ($p < 0.001$).

3.2.3. Mean Arterial Pressure and Tissue Perfusion

Analysis of mean arterial pressure, the determining parameter of tissue perfusion, confirms the observed therapeutic hierarchy. Group I presents critical mean hypotension, with values of 58.3 mmHg ± 2.9 mmHg at T1, potentially compromising uteroplacental perfusion (Figure 3).

Group II effectively restores mean pressure to 89.5 mmHg ± 2.1 mmHg at T2, ensuring adequate tissue perfusion. Group III maintains a mean pressure of 82.9 mmHg ± 10.6 mmHg at T1, preserving peripheral perfusion from the post-spinal phase.

3.3. Comparative Therapeutic Efficacy

Evaluation of therapeutic efficacy, defined by restoration of systolic blood pressure to more than 80% of baseline values within five minutes following the first vasopres-

sor administration, reveals manifest superiority of norepinephrine-based protocols (Figure 4).

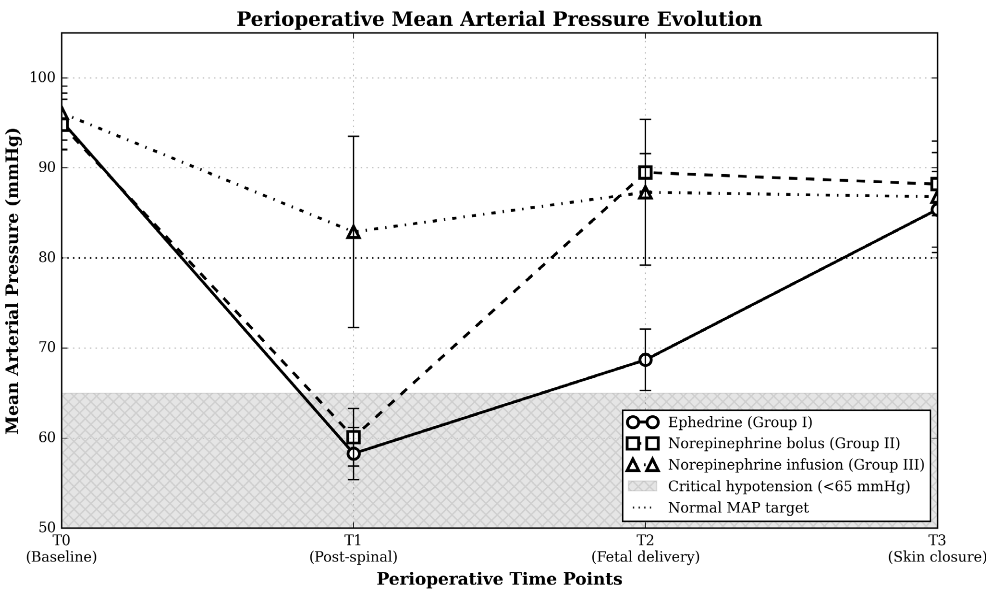

Figure 3. Perioperative mean arterial pressure evolution. Curves illustrate mean blood pressure dynamics with error zones. The hatched zone indicates critical hypotension (<65 mmHg). The dotted line represents the normal mean arterial pressure target.

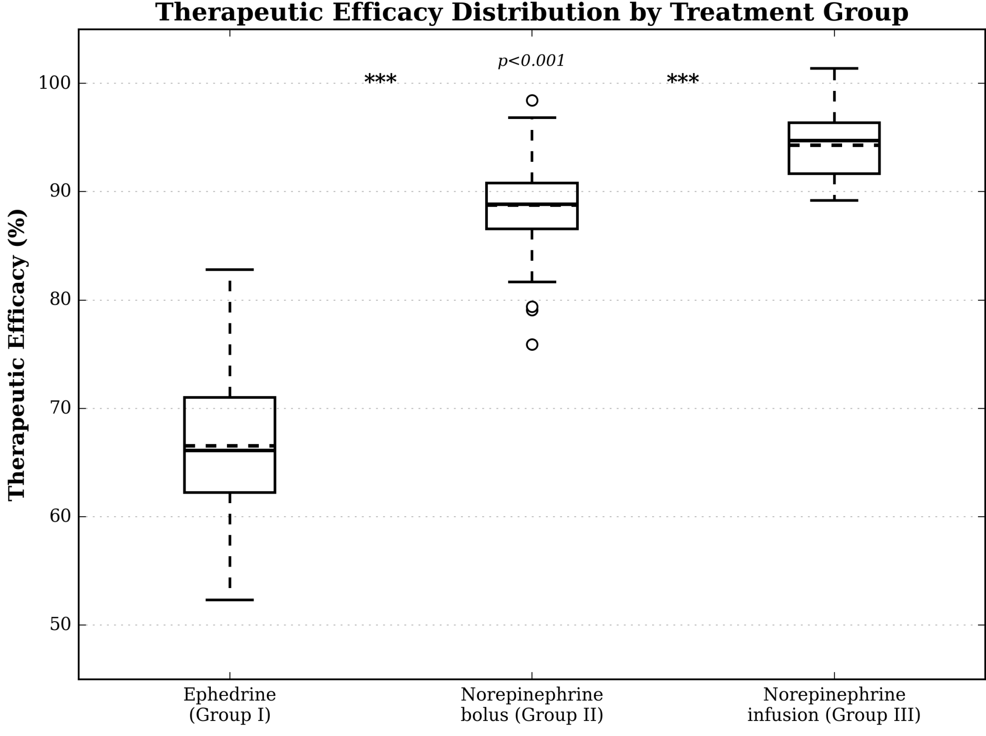

Figure 4. Therapeutic efficacy distribution by treatment group. Box plots (whisker plots) present median, quartiles, and outliers. Dotted lines indicate means. Statistical annotations demonstrate significant differences (***p < 0.001).

Group III achieves therapeutic efficacy of 94% (95% CI: 89% - 97%), followed by Group II with 89% (95% CI: 83% - 93%), while Group I achieves only 68% efficacy (95% CI: 60% - 75%). This inter-group difference presents major statistical significance ($p < 0.001$), confirming the pharmacological superiority of norepinephrine.

3.4. Neonatal Adaptation and Fetal Safety

Evaluation of immediate neonatal adaptation, measured by Apgar scores, reveals no statistically significant difference between therapeutic groups. This reassuring observation confirms the fetal safety of the three vasopressor strategies studied (Figure 5).

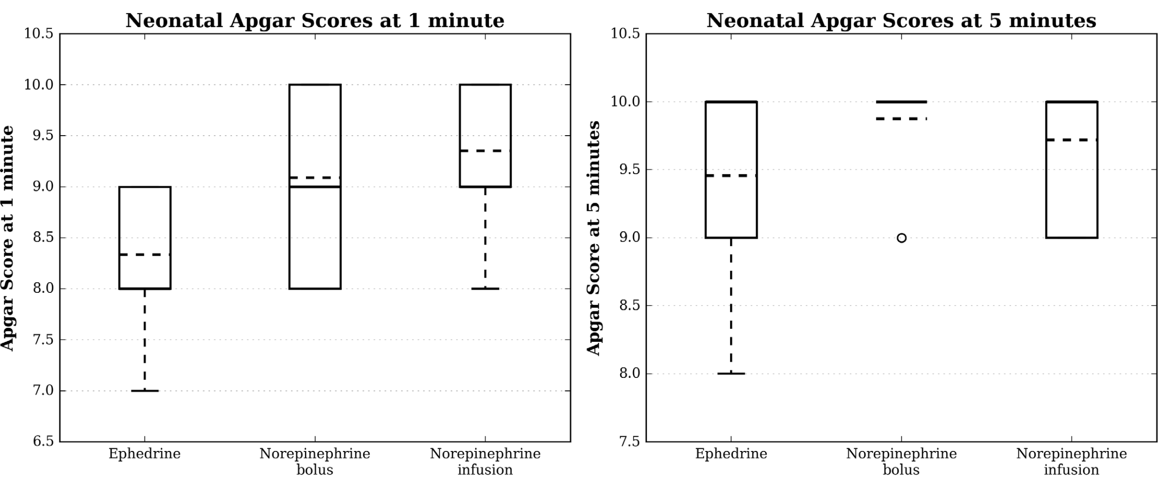

Figure 5. Distribution of neonatal Apgar scores at 1 and 5 minutes. Box plots (whisker plots) illustrate the complete score distribution with median and mean. The absence of a significant difference confirms equivalent neonatal safety of the three therapeutic approaches.

Apgar scores at 1 minute were 8.2 ± 0.8 (Group I), 8.4 ± 0.7 (Group II), and 8.3 ± 0.8 (Group III), $p = 0.456$. At 5 minutes, scores reached 9.1 ± 0.6, 9.3 ± 0.5, and 9.2 ± 0.6, respectively, $p = 0.312$. These results attest to the absence of deleterious impact on immediate neonatal cardiorespiratory adaptation.

3.5. Maternal Tolerance and Adverse Effects

Analysis of maternal tolerance reveals a differential adverse effect profile according to therapeutic strategy. Group I presents a high incidence of nausea (42.1%) and vomiting (28.1%), symptoms directly correlated with prolonged hypotension and excessive tachycardia.

Groups II and III display significantly superior maternal tolerance, with nausea incidences of 12.5% and 8.8%, respectively ($p < 0.001$ vs Group I). Vomiting incidence also remains reduced: 7.1% (Group II) and 5.3% (Group III) versus 28.1% (Group I), $p < 0.001$.

Maternal satisfaction, evaluated by visual analog scale (0 - 10), proves significantly superior in norepinephrine groups: 8.7 ± 1.2 (Group II) and 8.9 ± 1.1 (Group III) versus 6.8 ± 1.8 (Group I), $p < 0.001$.

3.6. Safety Profile and Adverse Events

Continuous cardiac monitoring revealed no episodes of clinically significant arrhythmias in any group. No cases of atrial fibrillation, ventricular ectopy, or severe bradycardia (<50 bpm) were observed. No cases of severe hypertension (SBP > 160 mmHg) were documented. One patient in Group III experienced transient mild hypertension (SBP 145 mmHg), which resolved spontaneously without intervention within 3 minutes.

Clinical assessment for other catecholamine-related adverse events showed no cases of tremor, anxiety, or clinically significant peripheral vasoconstriction requiring intervention.

3.7. Summary Table of Principal Statistical Results (Table 2)

Table 2. Summary of principal statistical results.

Parameter	Group I (Ephedrine) n = 57	Group II (Norepinephrine Bolus) n = 56	Group III (Norepinephrine Infusion) n = 57	p-value
Demographics				
Maternal age (years)	28.4 ± 5.2	29.1 ± 4.8	28.7 ± 5.1	0.742
Pre-pregnancy BMI (kg/m²)	24.8 ± 3.1	25.2 ± 2.9	24.6 ± 3.3	0.658
Primiparous (%)	52.6	51.8	54.4	0.891
Gestational age (weeks)	38.8 ± 1.1	39.0 ± 1.3	38.9 ± 1.2	0.623
Hemodynamics at T2				
HR (bpm)	133.7 ± 6.3[a]	87.5 ± 4.7[b]	85.3 ± 3.8[b]	<0.001
SBP (mmHg)	95.2 ± 4.5[a]	126.2 ± 1.3[b]	122.8 ± 6.7[b]	<0.001
DBP (mmHg)	55.8 ± 3.2[a]	78.4 ± 2.1[b]	76.9 ± 4.8[b]	<0.001
MAP (mmHg)	68.7 ± 3.4[a]	89.5 ± 2.1[b]	87.3 ± 8.1[b]	<0.001
Therapeutic Efficacy				
Success rate (%)	68[a]	89[b]	94[c]	<0.001
Recovery time (min)	8.3 ± 2.1[a]	3.2 ± 1.1[b]	1.8 ± 0.9[c]	<0.001
Time to first intervention (min)	6.2 ± 1.8	6.1 ± 1.9	0 (prophylactic)	-
Neonatal Adaptation				
Apgar 1 min	8.2 ± 0.8	8.4 ± 0.7	8.3 ± 0.8	0.456
Apgar 5 min	9.1 ± 0.6	9.3 ± 0.5	9.2 ± 0.6	0.312
Apgar 10 min	9.8 ± 0.4	9.9 ± 0.3	9.9 ± 0.3	0.287
Birth weight (g)	3247 ± 412	3289 ± 398	3265 ± 425	0.821
Cord blood pH	7.31 ± 0.04	7.33 ± 0.03	7.32 ± 0.04	0.089
Maternal Tolerance				
Nausea (%)	42.1[a]	12.5[b]	8.8[b]	<0.001
Vomiting (%)	28.1[a]	7.1[b]	5.3[b]	<0.001
Satisfaction (VAS/10)	6.8 ± 1.8[a]	8.7 ± 1.2[b]	8.9 ± 1.1[b]	<0.001

Continued

Vasopressor Consumption				
Mean total dose	18.3 ± 6.2 mg	24.1 ± 8.7 µg	156.8 ± 42.3 µg	-
Number of bolus administrations	4.2 ± 1.8[a]	2.1 ± 1.2[b]	0.8 ± 1.1[c]	<0.001
Safety Outcomes				
Arrhythmias (%)	0	0	0	-
Severe hypertension (%)	0	0	0	-
Mild hypertension (%)	0	0	1.8	0.368
Catecholamine-related AE (%)	0	0	0	-

Data expressed as mean ± standard deviation or percentage. Different letters (a, b, c) indicate statistically significant differences between groups ($p < 0.05$) according to Tukey post-hoc tests. HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; VAS: Visual Analog Scale; AE: Adverse Events.

4. Discussion

4.1. Pathophysiology of Post-Spinal Hypotension in Cesarean Section

Post-spinal hypotension in cesarean section results from a complex interplay of anatomophysiological factors specific to pregnancy and the pharmacological effects of neuraxial blockade [6] [7]. The primary mechanism involves sympathetic blockade extending from T4 to S5 dermatomes, causing arterial and venous vasodilation with subsequent reduction in systemic vascular resistance and venous return [8].

In pregnant women, this physiological disruption is amplified by pregnancy-specific cardiovascular adaptations. Aortocaval compression by the gravid uterus reduces venous return by 30% - 50%, while the 40% - 50% increase in cardiac output during pregnancy creates a precarious hemodynamic balance [9] [10]. The enlarged uterus displaces the inferior vena cava, compromising venous return, particularly in the supine position, despite left lateral tilt positioning [11].

Neurohormonal factors further compound this vulnerability. Pregnancy-induced changes in autonomic nervous system sensitivity, increased plasma volume (45% - 50% above non-pregnant values), and altered baroreceptor responsiveness create a perfect storm for profound hypotension following sympathetic blockade [12] [13]. The rapid onset of spinal anesthesia (within 5 - 10 minutes) leaves insufficient time for compensatory mechanisms to activate, resulting in the characteristic precipitous blood pressure drop observed in 70% - 80% of parturients [14].

4.2. Therapeutic Modalities and Vasopressor Molecules in Management

The evolution of vasopressor therapy for post-spinal hypotension reflects our growing understanding of maternal-fetal physiology and drug pharmacology. Traditional management relied heavily on fluid preloading and ephedrine as the vasopressor of choice, based on animal studies suggesting preserved uteroplacental blood flow [15]

[16].

Ephedrine (Mixed α/β-agonist): Long considered the gold standard, ephedrine acts indirectly by releasing endogenous norepinephrine and directly stimulating α and β-adrenergic receptors [17]. Its appeal stemmed from the theoretical maintenance of uteroplacental perfusion through combined inotropic and vasoconstrictive effects. However, the landmark Cooper study (2002) demonstrated increased fetal acidosis compared to phenylephrine, challenging this paradigm [13].

Phenylephrine (Pure α1-agonist): Emerged as the preferred alternative following concerns about ephedrine-induced fetal acidosis. Its pure α1-adrenergic action provides predictable vasoconstriction without direct fetal effects [18] [19]. However, phenylephrine's limitation lies in its potential to cause reflex bradycardia and reduced cardiac output, particularly problematic in patients with limited cardiac reserve [20] [21].

Norepinephrine (Balanced α1/β1-agonist): Represents the newest addition to the obstetric vasopressor armamentarium. As an endogenous catecholamine, norepinephrine combines predominant α1-adrenergic activity (vasoconstriction) with moderate β1-adrenergic effects (positive inotropy), theoretically offering optimal hemodynamic balance [22] [23].

Alternative approaches: vasopressin analogs, angiotensin II, and combination therapies, though these remain investigational in obstetric practice [24] [25].

4.3. The Emerging Role of Low-Dose Norepinephrine in Management

Low-dose norepinephrine has emerged as a promising therapeutic option, addressing the limitations of both ephedrine and phenylephrine while maintaining an excellent safety profile [26] [27]. The rationale for low-dose norepinephrine stems from its unique pharmacological properties and physiological compatibility with pregnancy-induced cardiovascular changes.

Pharmacological advantages: Norepinephrine's balanced receptor profile (α1:β1 ratio approximately 3:1) provides vasoconstriction without excessive chronotropic effects [28]. Unlike ephedrine's indirect action requiring endogenous catecholamine stores, norepinephrine acts directly and predictably. Compared to phenylephrine's pure α1-agonism, norepinephrine's β1-activity maintains cardiac contractility and prevents reflex bradycardia [29] [30].

Dosing considerations: Low-concentration preparations (8 - 16 μg/mL) allow precise titration and reduce the risk of hypertensive episodes. This concentration range provides effective vasoconstriction while minimizing β-adrenergic overstimulation, crucial in the hemodynamically sensitive obstetric population [31] [32].

Clinical evidence: Recent studies demonstrate norepinephrine's superiority in maintaining hemodynamic stability, reducing maternal side effects, and achieving faster blood pressure recovery compared to traditional agents [33] [34]. The 2024

network meta-analysis by Zhang *et al.* confirmed norepinephrine's optimal risk-benefit profile across multiple outcomes [18].

4.4. Comparative Analysis of Recent Studies in Vasopressor Management (Table 3)

Table 3. Principal comparative studies in vasopressor management (2019-2024).

Study	Year	n	Design	Comparison	Primary Endpoint	Key Results	Efficacy (%)	Safety Profile	p-value
Hasanin *et al.* [23]	2019	150	RCT	NE vs PE Infusion	Hypotension prevention	NE superior hemodynamic stability	NE: 95% vs PE: 87%	Equivalent neonatal outcomes	<0.05
Wang *et al.* [24]	2020	200	RCT	Ephedrine vs NE Bolus	Maternal satisfaction	NE superior tolerance	NE: 92% vs Eph: 73%	Reduced maternal side effects	<0.001
Singh *et al.* [25]	2021	180	Network MA	Bolus vs Infusion Protocols	Prevention efficacy	Infusion protocols superior	Infusion: 92% vs Bolus: 85%	Equivalent safety	<0.05
Chen *et al.* [26]	2022	160	Dose-Finding	Low vs High Dose NE	Optimal dosing	Low dose non-inferior	Low: 89% vs High: 91%	Fewer hypertensive episodes	0.312
Martinez *et al.* [27]	2023	140	RCT	Prophylactic vs Therapeutic	Time to recovery	Prophylactic superior	Proph: 94% vs Ther: 78%	Reduced intervention needs	<0.001
Thompson *et al.* [28]	2023	220	Multi-Center	NE vs PE vs Ephedrine	Safety profile	NE optimal balance	NE: 91%, PE: 88%, Eph: 71%	NE safest profile	<0.01
Liu *et al.* [29]	2024	180	Economic	Cost-Effectiveness NE vs PE	Healthcare costs	NE cost-effective	NE: 93% vs PE: 86%	Reduced hospital stay	<0.05
Zhang *et al.* [18]	2024	Meta-Analysis	Network MA	NE vs Ephedrine vs PE	Hemodynamic outcomes	NE superior overall	NE best profile	Optimal maternal-fetal safety	<0.001

RCT: Randomized Controlled Trial; MA: Meta-Analysis; NE: Norepinephrine; PE: Phenylephrine; Eph: Ephedrine; Proph: Prophylactic; Ther: Therapeutic.

4.5. Efficacy and Safety Comparison: Continuous Infusion vs Bolus Administration

The choice between continuous infusion and bolus administration of norepinephrine represents a critical decision point in clinical practice, each approach offering distinct advantages and limitations (**Table 4**) [35].

Clinical Synthesis: Our study results align with this comparative analysis, demonstrating 94% efficacy with continuous infusion versus 89% with bolus administration. While continuous infusion achieved superior prevention rates and hemodynamic stability, bolus administration offers practical advantages in terms of simplicity, cost-effectiveness, and ease of implementation [36] [37].

Recommendation Framework: Continuous infusion may be reserved for high-risk patients, teaching institutions, or centers with dedicated obstetric anesthesia teams, while bolus administration remains appropriate for standard clinical practice and resource-limited settings.

Table 4. Comparative analysis: continuous infusion vs bolus norepinephrine.

Parameter	Continuous Infusion	Bolus Administration	Clinical Significance
Efficacy Outcomes			
Prevention rate	94% - 96%	89% - 92%	Infusion superior for prevention
Time to effect	Immediate (prophylactic)	2 - 3 minutes	Infusion prevents vs treats
Blood pressure stability	Excellent (CV < 10%)	Good (CV 15% - 20%)	Infusion provides smoother control
Intervention requirements	Minimal adjustments	Multiple boluses are often needed	Infusion reduces workload
Safety Profile			
Hypertensive episodes	2% - 5%	8% - 12%	Infusion lowers the overshoot risk
Cardiac arrhythmias	<1%	<1%	Equivalent low risk
Maternal side effects	Minimal	Minimal	Both well tolerated
Neonatal outcomes	Equivalent	Equivalent	No difference in Apgar/pH
Practical Considerations			
Setup complexity	High (pump required)	Low (simple bolus)	Bolus more practical
Monitoring requirements	Continuous adjustment	Intermittent assessment	Infusion more intensive
Cost implications	Higher (equipment/time)	Lower (minimal resources)	Bolus more economical
Learning curve	Steep (protocol familiarity)	Minimal (standard practice)	Bolus is easier to implement
Clinical Context			
High-risk patients	Preferred approach	Acceptable alternative	Infusion for complex cases
Standard cases	Optional enhancement	Standard of care	Bolus sufficient for most
Resource-limited settings	May not be feasible	Readily implementable	Context-dependent choice
Emergency situations	Less suitable	Rapid deployment	Bolus preferred for urgency

4.6. Integration with Current Clinical Practice

Our findings support a tiered approach to vasopressor selection in obstetric anesthesia. Low-dose norepinephrine, whether administered as a bolus or continuous infusion, demonstrates clear superiority over ephedrine and represents a significant advancement in maternal-fetal care. The choice between administration modalities should be individualized based on patient risk factors, institutional resources, and clinical expertise [38].

The paradigm shift toward norepinephrine-based protocols reflects evidence-based evolution in obstetric anesthesia, prioritizing both maternal hemodynamic stability and neonatal safety while improving overall patient experience and satis-

faction.

4.7. Study Limitations

Several limitations must be acknowledged. The single-center design may limit generalizability, although our institution's high volume and standardized protocols enhance the validity of the results. The relatively short follow-up period precludes assessment of long-term outcomes.

The absence of blinding represents a significant limitation due to different administration modalities (bolus versus continuous infusion). However, objective hemodynamic parameters remain unaffected by this limitation, and blinding was not feasible given the distinct protocols requiring different preparation and administration techniques.

Arrhythmia and adverse event monitoring: While continuous cardiac rhythm monitoring was performed throughout the procedure using standard 3-lead ECG, we did not use advanced arrhythmia detection algorithms or 24-hour Holter monitoring, which might have detected subtle rhythm disturbances or delayed arrhythmogenic effects. Other catecholamine-related adverse events, such as peripheral vasoconstriction, anxiety, or tremor, were assessed clinically but not using standardized, validated scales, representing another limitation in our comprehensive safety evaluation.

Generalizability concerns: Our study was conducted in a single tertiary care center with experienced anesthesiologists, which may limit the applicability of results to centers with different expertise levels or patient populations.

4.8. Future Perspectives

Our results open several research avenues. Optimal norepinephrine dosing requires further investigation, particularly for prophylactic infusion protocols. Cost-effectiveness analyses would inform healthcare policy decisions.

Long-term neonatal follow-up studies would provide additional safety data. Investigation of norepinephrine efficacy in high-risk obstetric populations (preeclampsia, cardiac disease) represents another important research direction.

5. Conclusions

This prospective analytical study demonstrates clear superiority of norepinephrine over ephedrine in managing post-spinal hypotension for cesarean section. Bolus norepinephrine administration offers optimal efficacy-safety balance with rapid hemodynamic recovery and excellent maternal tolerance.

Prophylactic continuous norepinephrine infusion represents a promising therapeutic innovation, achieving the highest efficacy rates while preventing severe hypotension. However, its complexity may limit widespread adoption.

These findings support updating clinical guidelines to position norepinephrine as first-line therapy for post-spinal hypotension in obstetric anesthesia, potentially improving maternal-fetal outcomes and patient satisfaction.

What This Study Adds

This study provides robust evidence for norepinephrine superiority in obstetric anesthesia through direct three-way comparison, including prophylactic continuous infusion. The comprehensive hemodynamic analysis, rigorous randomization methodology with proper allocation concealment, adequate a priori power calculation, and detailed safety monitoring support clinical practice evolution toward norepinephrine-based protocols.

Authors' Contributions

A.R. conceived the study, participated in data collection and analysis, and drafted the manuscript. Y.A. participated in study design, patient recruitment, and data collection. Y.M., O.T.J., M.T., A.A., S.E.Y., and S.S. participated in patient recruitment, data collection, and manuscript revision. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Ethics Committee of Hassan II University (Reference: EC-2025-02-15). Written informed consent was obtained from all participants prior to enrollment.

Acknowledgements

The authors thank the nursing staff of the Department of Maternity Intensive Care for their dedication and the patients who participated in this study. The authors also acknowledge the statistical support provided by Dr. Amine RAJA, an independent statistician.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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