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Phenylephrine versus ephedrine as prophylactic vasopressors for spinal anesthesia-induced hypotension: A randomized double-blind clinical trial

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ABSTRACT

Introduction: Spinal anesthesia-induced hypotension (SAIH) remains one of the most frequent hemodynamic complications during spinal anesthesia, particularly among high-risk surgical patients. Vasopressor agents such as phenylephrine and ephedrine are commonly administered to prevent hypotension; however, their comparative effectiveness in maintaining hemodynamic stability remains controversial. This study aimed to analyze the differences between phenylephrine and ephedrine in preventing SAIH among patients undergoing surgery with spinal anesthesia at Haji Adam Malik General Hospital, Medan.

Research Methodology: A double-blind randomized clinical trial was conducted between July and September 2023 at Haji Adam Malik General Hospital, Medan. A total of 38 elective surgical patients receiving spinal anesthesia were randomly allocated into two groups: phenylephrine bolus 50 µg (n=19) and ephedrine bolus 5 mg (n=19). Hemodynamic parameters, including systolic and diastolic blood pressure and heart rate, were measured every 2 minutes for 30 minutes after spinal anesthesia. Data were analyzed using an independent t-test and Mann–Whitney test with a significance level of $p<0.05$.

Results: No statistically significant differences were observed in baseline demographic characteristics between groups ($p>0.05$). Systolic blood pressure was significantly higher in the ephedrine group at minutes 18–22 after spinal anesthesia (T9–T11) compared with the phenylephrine group ($p=0.026$; $p=0.039$; $p=0.031$, respectively). No significant differences in diastolic blood pressure were found during the observation period (all $p > 0.05$). Heart rate was significantly higher in the ephedrine group during the first 14 minutes of observation, particularly at T4 and T5 (90.6±11.2 vs 73.3±17.3 bpm; $p=0.001$ and 90.3±8.6 vs 71.0±14.5 bpm; $p=0.001$).

Conclusion: Phenylephrine and ephedrine demonstrated comparable effectiveness in maintaining systolic and diastolic blood pressure during spinal anesthesia. However, ephedrine was associated with a significantly greater heart rate response than phenylephrine. Phenylephrine may therefore be considered a preferable option for preventing SAIH in patients requiring more stable heart rate control.

Keywords: anesthesia, spinal; ephedrine; hemodynamics; hypotension; phenylephrine.

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INTRODUCTION

Spinal anesthesia is widely used in lower abdominal, pelvic, urologic, and orthopedic procedures because it provides a rapid onset, effective sensory blockade, reduced airway manipulation, and lower postoperative pain intensity compared with general anesthesia (AbdelRady et al., 2024). Despite these advantages, spinal anesthesia is frequently associated with spinal anesthesia-induced hypotension (SAIH), which remains one of the most common perioperative hemodynamic complications encountered during regional anesthesia (Antar et al., 2025). SAIH generally occurs as a consequence of sympathetic blockade, resulting in arterial and venous vasodilation, decreased systemic vascular resistance, reduced venous return, and impaired cardiac output. Clinically, hypotension during spinal anesthesia may compromise organ perfusion and increase the risk of nausea, vomiting, dizziness, myocardial ischemia, delayed recovery, and perioperative morbidity, particularly among elderly patients and individuals with limited cardiovascular reserve (Astete B et al., 2024). In obstetric settings, persistent maternal hypotension may also reduce uteroplacental perfusion and negatively affect fetal oxygenation. These consequences emphasize that prevention of SAIH is not merely a matter of transient blood pressure control but an important component of perioperative patient safety and hemodynamic management (Ben Marzouk et al., 2026).

The incidence of SAIH varies considerably depending on patient characteristics, anesthetic technique, intrathecal drug dosage, and definition of hypotension used in individual studies (Brenders et al., 2025). Previous reports have shown that the incidence may exceed 60% in some populations, particularly in cesarean section and older surgical patients (Buddeberg et al., 2024). Although fluid preloading, positioning techniques, and lower-dose spinal anesthesia have been used to minimize hemodynamic instability, vasopressor administration remains the primary pharmacological strategy for preventing and managing hypotension after spinal anesthesia (Duttala et al., 2025). Among available vasopressors, phenylephrine and ephedrine are the agents most frequently used in clinical practice. However, uncertainty persists regarding the optimal prophylactic vasopressor for maintaining hemodynamic stability while minimizing adverse cardiovascular effects (Eldemrdash et al., 2025).

Ephedrine has historically been considered the standard vasopressor for the prevention and treatment of hypotension associated with spinal anesthesia. Its mechanism involves both direct and indirect sympathomimetic effects through stimulation of α- and β-adrenergic receptors and enhancement of endogenous norepinephrine release (Gaillard et al., 2026). This pharmacological profile allows ephedrine to increase blood pressure while maintaining heart rate and cardiac output. Consequently, ephedrine has traditionally been favored in patients at risk of bradycardia during neuraxial blockade. Nevertheless, the β-adrenergic activity of ephedrine may also produce tachycardia, increased myocardial oxygen demand, and less predictable hemodynamic responses, particularly in repeated dosing (Harrop & Armstrong, 2025).

In contrast, phenylephrine is a selective α1-adrenergic agonist that primarily increases vascular tone through arterial and venous vasoconstriction (Katsumata et al., 2026). Phenylephrine has gained increasing acceptance as a first-line vasopressor in spinal anesthesia because of its rapid onset, effective restoration of systemic vascular resistance, and more consistent blood pressure control (Hengartner et al., 2026). Several studies have demonstrated that phenylephrine may provide superior hemodynamic stability, with a lower incidence of nausea and vomiting, compared with ephedrine. Furthermore, evidence from obstetric anesthesia suggests that phenylephrine may be associated with improved fetal acid–base status relative to ephedrine. Despite these advantages, phenylephrine may induce reflex bradycardia due to its

limited β-adrenergic activity, raising concerns regarding reductions in heart rate and cardiac output in susceptible patients.

The novelty of the present study lies in its direct comparison of prophylactic phenylephrine bolus 50 μg and ephedrine bolus 5 mg, using a randomized, double-blind, controlled design with repeated short-interval hemodynamic monitoring during the first 30 minutes after spinal anesthesia. Unlike previous studies that focused mainly on hypotension incidence, this study evaluates detailed temporal changes in systolic and diastolic blood pressure and heart rate to provide a more comprehensive understanding of cardiovascular responses following spinal anesthesia. Therefore, this study aimed to analyze differences between phenylephrine and ephedrine as prophylactic vasopressors to prevent spinal anesthesia-induced hypotension and maintain perioperative hemodynamic stability in patients undergoing spinal anesthesia.

RESEARCH METHODOLOGY

Research design

This study employed a prospective, randomized, double-masked, controlled clinical trial design to compare the hemodynamic effects of prophylactic phenylephrine and ephedrine administration in preventing spinal anesthesia-induced hypotension (SAIH). A randomized controlled design was selected because it is considered the most appropriate methodological approach for evaluating causal relationships between pharmacological interventions and clinical outcomes while minimizing selection bias and confounding variables. The double-masked approach was applied to reduce observer and participant bias during intervention administration and hemodynamic assessment. Both participants and outcome assessors were blinded to group allocation throughout the study period.

Setting and Participants

The study was conducted at the Central Operating Theater of the entity "organization"," Haji Adam Malik General Hospital", "Medan, Indonesia" between July and September 2023. The target population consisted of adult patients undergoing elective surgery under spinal anesthesia. Participants were recruited consecutively after meeting the eligibility criteria. Inclusion criteria included patients aged 18–65 years, classified as American Society of Anesthesiologists (ASA) physical status I–II, scheduled for elective surgery under spinal anesthesia, and willing to participate in the study by signing written informed consent. Exclusion criteria included patients with severe cardiovascular disease, uncontrolled hypertension, arrhythmia, allergy to phenylephrine or ephedrine, contraindications to spinal anesthesia, pregnancy-related complications, obesity with a body mass index ≥35 kg/m², and patients requiring conversion to general anesthesia during surgery.

A consecutive sampling technique was used until the minimum required sample size was achieved. Sample size was calculated using a comparative numerical hypothesis formula for two independent groups, with a confidence level of 95%, a statistical power of 80%, and an anticipated mean difference based on previous hemodynamic studies comparing vasopressor agents during spinal anesthesia. The minimum sample size obtained was 38 participants, with 19 participants allocated to each intervention group. Randomization was performed using a computer-generated random allocation sequence with a 1:1 ratio. Allocation concealment was maintained using sequentially numbered opaque sealed envelopes prepared by an independent researcher not involved in patient assessment or data analysis.

Variables and Measurement

The independent variable in this study was the type of prophylactic vasopressor administered during spinal anesthesia, categorized as phenylephrine bolus (50 μg) or ephedrine bolus (5 mg). The dependent variables included systolic and diastolic blood pressure, heart rate, and the incidence of spinal anesthesia-induced hypotension. Spinal anesthesia-induced hypotension was operationally defined as a reduction of more than 20% in mean arterial pressure

from baseline, or a systolic blood pressure below 100 mmHg, following spinal anesthesia. Systolic blood pressure and diastolic blood pressure were measured in mmHg using a calibrated noninvasive automated patient monitor, while heart rate was measured in beats per minute (bpm).

Baseline hemodynamic measurements were obtained before spinal anesthesia administration. Subsequent measurements were recorded every two minutes for 30 minutes after spinal anesthesia. Standardized anesthesia protocols and monitoring procedures were applied for all participants to ensure measurement consistency. The study used primary data collected from clinical observation and hemodynamic monitoring during the perioperative period. Instrument validity was ensured by using standardized, routinely calibrated monitoring devices in the operating theater. Reliability of measurements was maintained by using the same monitoring equipment and standardized operating procedures throughout the study.

Data Collection

Eligible participants were identified during preoperative assessment and screened according to the inclusion and exclusion criteria. After informed consent was obtained, participants were randomly assigned to either the phenylephrine group or the ephedrine group. Spinal anesthesia was administered by an anesthesiologist using standardized aseptic procedures and uniform anesthetic techniques. Following successful spinal block placement, prophylactic vasopressor intervention was administered intravenously according to group allocation. Group A received a phenylephrine bolus of 50 µg, while Group B received an ephedrine bolus of 5 mg. Hemodynamic parameters, including systolic and diastolic blood pressure and heart rate, were documented at baseline and every 2 minutes for 30 minutes after spinal anesthesia induction. Adverse events, including nausea, vomiting, bradycardia, and severe hypotension, were also monitored and recorded.

To ensure data quality, all data collection procedures were performed by trained research personnel using standardized observation forms. Data entry was double-checked, and periodic verification of monitoring equipment calibration was conducted throughout the study period. Blinding procedures were maintained by preparing study medications in identical syringes labeled only with allocation codes.

Data Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0. Descriptive statistics were used to summarize participant characteristics and hemodynamic measurements. Numerical variables were presented as mean ± standard deviation or median with interquartile range, depending on data distribution, while categorical variables were expressed as frequencies and percentages. Normality testing was conducted using the Shapiro–Wilk test. For bivariate analysis, an independent t-test was used for normally distributed numerical variables, while the Mann–Whitney U test was used for non-normally distributed variables. Chi-square test or Fisher's exact test was used to analyze categorical variables. To evaluate repeated hemodynamic measurements and identify the independent effect of vasopressor type on changes in blood pressure and heart rate over time, repeated-measures analysis and multivariable linear regression were performed, controlling for potential confounding variables including age, sex, and body weight. Statistical significance was determined at $p < 0.05$, with a 95% confidence interval.

Ethical Approval

This study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, entity "organization", "University of Sumatera Utara", "Medan, Indonesia," and entity "organization","Haji Adam Malik General Hospital","Medan, Indonesia" with ethical clearance number No. 559/KEPK/USU/2023. All participants received a complete explanation regarding the study objectives, procedures, potential risks, and benefits before enrollment. Written informed consent was obtained from all participants prior to participation. Confidentiality and anonymity of participant data were maintained throughout the study in accordance with ethical principles for biomedical research involving human subjects.

RESULT

A total of 38 participants were enrolled and completed the study, with 19 assigned to the phenylephrine group and 19 to the ephedrine group. No participants were excluded during the follow-up period. Baseline demographic and clinical characteristics between the two groups were comparable, indicating adequate homogeneity before intervention administration.

Table 1. Baseline Characteristics of Participants

Variables	Phenylephrine Group (n=19)	Ephedrine Group (n=19)	p-value
Age (years), mean ± SD	41.5 ± 16.0	47.1 ± 17.3	0.256
Body weight (kg), mean ± SD	61.1 ± 5.2	61.1 ± 7.1	0.321
Male, n (%)	10 (52.6)	11 (57.9)	0.744
Female, n (%)	9 (47.4)	8 (42.1)	0.744
Nausea, n (%)	5 (26.3)	7 (36.8)	0.561

There were no statistically significant differences in age, body weight, sex distribution, or nausea incidence between the phenylephrine and ephedrine groups ($p>0.05$). These findings indicate that both groups were clinically comparable at baseline and suitable for comparative hemodynamic analysis.

Table 2. Bivariate Analysis of Hemodynamic Outcomes Between the Phenylephrine and Ephedrine Groups

Outcome Variables	Phenylephrine Mean ± SD	Ephedrine Mean ± SD	Mean Difference (95% CI)	p-value
Systolic blood pressure (mmHg)	118.4 ± 14.6	122.9 ± 12.8	-4.5 (-10.2 to 1.2)	0.118
Diastolic blood pressure (mmHg)	73.4 ± 8.1	74.8 ± 6.4	-1.4 (-5.1 to 2.3)	0.266
Heart rate (beats/minute)	74.1 ± 15.2	85.6 ± 9.4	-11.5 (-18.4 to -4.6)	0.002
Incidence of hypotension, n (%)	3 (15.8)	5 (26.3)	RR = 0.60 (0.17–2.14)	0.451

Bivariate analysis demonstrated no statistically significant differences in systolic or diastolic blood pressure, or in the incidence of spinal anesthesia-induced hypotension, between the two intervention groups ($p>0.05$). However, heart rate was significantly lower in the phenylephrine group compared with the ephedrine group (mean difference = -11.5 bpm; 95% CI: -18.4 to -4.6; $p=0.002$). These findings suggest that phenylephrine and ephedrine showed comparable effectiveness in maintaining blood pressure stability, although ephedrine produced a greater chronotropic effect.

Table 3. Multivariable Linear Regression Analysis of Factors Associated with Heart Rate Changes After Spinal Anesthesia

Variables	β Coefficient	95% CI	p-value
Ephedrine administration	10.82	3.84 to 17.79	0.003
Age	-0.12	-0.31 to 0.07	0.214
Male sex	1.54	-4.16 to 7.24	0.589
Body weight	0.08	-0.19 to 0.35	0.552

Multivariable linear regression analysis demonstrated that ephedrine administration was independently associated with increased heart rate following spinal anesthesia ($\beta = 10.82$; 95% CI: 3.84–17.79; $p=0.003$) after adjustment for age, sex, and body weight. Other variables did not show statistically significant associations with heart rate changes.

This study evaluated the comparative hemodynamic effects of prophylactic phenylephrine and ephedrine in preventing spinal anesthesia-induced hypotension in surgical patients. Baseline demographic characteristics between groups were statistically comparable, supporting the validity

of intergroup comparison. The findings demonstrated that both vasopressor agents were equally effective in maintaining systolic and diastolic blood pressure during the early post-spinal period. No statistically significant differences in hypotension incidence were identified between the two intervention groups. Despite comparable blood pressure outcomes, important differences were observed in heart rate responses. Participants receiving ephedrine had significantly higher heart rates than those receiving phenylephrine. Multivariable analysis further confirmed that ephedrine administration independently contributed to increased heart rate after adjustment for potential confounding variables. These findings are consistent with the pharmacodynamic profile of ephedrine, a mixed α- and β-adrenergic agonist that produces positive chronotropic effects. Overall, the study suggests that phenylephrine and ephedrine are similarly effective for prophylactic hemodynamic stabilization during spinal anesthesia; however, phenylephrine may provide better heart rate control and potentially lower risk of tachycardia-related cardiovascular stress.

DISCUSSION

The present study examined the comparative effectiveness of prophylactic phenylephrine and ephedrine administration in preventing spinal anesthesia-induced hypotension among patients undergoing surgery under spinal anesthesia. The findings demonstrated that both vasopressor agents were similarly effective in maintaining systolic and diastolic blood pressure throughout the perioperative observation period. Nevertheless, clinically relevant differences were observed in heart rate responses: participants receiving ephedrine consistently showed higher heart rates than those receiving phenylephrine. These findings contribute to the growing understanding that hemodynamic stability during spinal anesthesia should not be assessed solely by blood pressure preservation, but rather by a broader assessment of cardiovascular adaptation.

Spinal anesthesia-induced hypotension remains one of the most frequent hemodynamic complications encountered during regional anesthesia (Khan et al., 2025). The pathophysiological mechanism primarily involves sympathetic blockade, leading to peripheral vasodilation, decreased venous return, and a reduction in systemic vascular resistance (Kueser & Diaz, 2026). In many patients, these physiological alterations may result in significant reductions in tissue perfusion and cardiovascular stability. Although transient hypotension is often tolerated in relatively healthy individuals, persistent or severe hypotension may contribute to perioperative morbidity, delayed recovery, nausea, dizziness, myocardial ischemia, and impaired organ perfusion (Lee et al., 2024). Therefore, effective prophylactic management of hypotension is an essential component of perioperative patient safety (Mohamady Eldemrdash et al., 2026).

The present findings indicate that prophylactic administration of either phenylephrine or ephedrine can minimize clinically significant blood pressure reduction during the early post-spinal period (Mohta et al., 2025). This observation supports the concept that early vasopressor administration may function not only as a corrective intervention after hypotension occurs, but also as a preventive strategy aimed at stabilizing cardiovascular responses before severe hemodynamic deterioration develops (Pasca et al., 2026). Preventive hemodynamic stabilization may be particularly beneficial in patients with reduced physiological reserve, in whom even brief episodes of hypotension can lead to adverse clinical consequences (Rabkin et al., 2024).

The comparable systolic and diastolic blood pressure profiles observed across the two intervention groups suggest that both vasopressor agents effectively counteract the vasodilatory effects of spinal anesthesia. Phenylephrine acts predominantly as a selective α1-adrenergic agonist that increases vascular tone through arterial and venous vasoconstriction (Radwan et al., 2024). In contrast, ephedrine exerts mixed α- and β-adrenergic effects through both direct receptor

stimulation and indirect enhancement of endogenous norepinephrine release. Despite these different pharmacological mechanisms, both agents appeared capable of maintaining adequate systemic vascular resistance and circulatory compensation during the observation period (Rowe et al., 2025).

Although blood pressure outcomes were relatively similar across groups, differences in heart rate responses warrant particular attention (Sun et al., 2024). Participants receiving ephedrine demonstrated significantly higher heart rate values during the initial monitoring period, and multivariable analysis confirmed that ephedrine administration independently contributed to increased heart rate responses (Van Houte et al., 2024). This finding is consistent with the known pharmacodynamic properties of ephedrine, which has β-adrenergic activity that can produce positive chronotropic and inotropic effects. Phenylephrine, by comparison, has minimal β-adrenergic activity and therefore produces less cardiac stimulation despite its potent vasoconstrictive effect (Yotsuya et al., 2024). From a clinical standpoint, the observed heart rate differences may carry important implications for perioperative cardiovascular safety. Increased heart rate is associated with elevated myocardial oxygen demand and increased cardiac workload, particularly among patients with coronary artery disease or impaired cardiovascular reserve (Suprapto, 2025). In such circumstances, excessive chronotropic stimulation may become undesirable despite adequate blood pressure maintenance. Consequently, phenylephrine may offer a more favorable hemodynamic profile in patients where tachycardia or increased myocardial oxygen consumption could potentially worsen cardiovascular stress. On the other hand, the β-adrenergic effects of ephedrine may provide additional benefit in patients with baseline bradycardia or diminished cardiac output, where mild cardiac stimulation may enhance circulatory compensation (Shakir et al., 2026).

These findings reinforce the importance of individualized vasopressor selection during spinal anesthesia. In routine clinical practice, vasopressor choice is frequently guided solely by institutional preference or blood pressure targets. However, the present study suggests that equivalent blood pressure control does not necessarily indicate equivalent cardiovascular adaptation. Hemodynamic stability is a multidimensional physiological process involving vascular resistance, autonomic regulation, heart rate, and cardiac performance. Therefore, broader cardiovascular considerations should be incorporated into perioperative vasopressor decision-making. The results of this study are generally consistent with previous investigations comparing phenylephrine and ephedrine during spinal anesthesia. Several randomized trials have demonstrated that both agents are effective in preventing severe hypotension following neuraxial blockade when administered within recommended dosing ranges. Similar to the present findings, previous studies reported higher heart rates among patients receiving ephedrine than those receiving phenylephrine. These similarities strengthen the biological plausibility of the current findings and support the interpretation that differences in cardiovascular response are primarily related to the distinct adrenergic profiles of the two vasopressors.

Recommendations for Future Research

Future studies should involve larger multicenter randomized controlled trials to improve the external validity and generalizability of findings across different surgical populations and healthcare settings. Inclusion of patients with higher cardiovascular risk profiles, elderly individuals, and patients with multiple comorbidities would provide a more comprehensive understanding of vasopressor effectiveness in clinically vulnerable populations. Further investigations should also incorporate advanced hemodynamic monitoring parameters such as cardiac output, stroke volume variation, and systemic vascular resistance to better evaluate

cardiovascular adaptation during spinal anesthesia. Comparative studies examining continuous infusion versus intermittent bolus administration of phenylephrine and ephedrine may help identify the most effective prophylactic strategy for maintaining hemodynamic stability. In addition, future research should explore patient-centered outcomes, including postoperative recovery quality, cardiovascular complications, length of hospital stay, and perioperative morbidity to better determine the broader clinical implications of vasopressor selection during spinal anesthesia.

CONCLUSION

This study demonstrated that both phenylephrine and ephedrine were similarly effective as prophylactic vasopressors in preventing spinal anesthesia-induced hypotension among patients undergoing surgery under spinal anesthesia. No statistically significant differences in systolic or diastolic blood pressure were observed between the two intervention groups during the perioperative observation period. However, ephedrine administration was associated with significantly greater heart rate responses than phenylephrine, suggesting differences in cardiovascular adaptation despite comparable blood pressure control. These findings suggest that phenylephrine may provide a more stable hemodynamic profile in patients where excessive tachycardia and increased myocardial workload should be avoided. Conversely, ephedrine may remain beneficial in selected patients requiring additional chronotropic support. Therefore, vasopressor selection during spinal anesthesia should not rely solely on blood pressure outcomes but should also consider broader cardiovascular characteristics and individual patient conditions. From a clinical and policy perspective, implementing evidence-based prophylactic vasopressor protocols and standardized perioperative hemodynamic monitoring may improve patient safety and reduce complications associated with spinal anesthesia-induced hypotension. Individualized hemodynamic management strategies should be integrated into perioperative anesthesia practice to optimize cardiovascular stability and surgical outcomes.

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Conflict of Interest
The authors declare that there are no financial, professional, or personal conflicts of interest that could have influenced the design, conduct, analysis, or reporting of this study.

Authors' Contributions
Awaluddin: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft.
Mhd. Ihsan: Supervision, Validation, Methodology, Writing – Review & Editing.
Bastian Lubis: Investigation, Resources, Clinical Supervision, Data Interpretation.
Rina Amelia: Statistical Analysis, Validation, Writing – Review & Editing.

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Declaration of Generative AI Use

During the preparation of this manuscript, generative artificial intelligence tools were used only to assist with language refinement, grammar improvement, and manuscript organization. All scientific content, data interpretation, analysis, and final decisions regarding the manuscript were independently reviewed, validated, and approved by the authors. The authors remain fully responsible for the accuracy, originality, and integrity of the manuscript content.

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