COMPARISON OF THE EFFECTIVENESS OF BOLUS DOSES OF NOREPINEPHRINE 4 MCG AND PHENILEPHRINE 50 MCG IN MANAGING HYPOTENSION AFTER SPINAL ANESTHESIA IN CESAREAN SECTION PATIENTS

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ABSTRACT

Background: Spinal anesthesia is the preferred method for cesarean sections but frequently causes maternal hypotension, posing risks to both mother and fetus. Phenylephrine has been the traditional vasopressor, but its association with reflex bradycardia raises concerns. Norepinephrine may offer a more stable hemodynamic response. This study compared the efficacy and safety of norepinephrine (4 mcg) and phenylephrine (50 mcg) bolus doses in managing spinal-induced hypotension during cesarean delivery.

Methods: A randomized, double-blind clinical trial was conducted with 46 parturients undergoing elective cesarean section under spinal anesthesia. Participants received either norepinephrine 4 mcg or phenylephrine 50 mcg intravenously upon hypotension onset. Hemodynamic parameters (SBP, DBP, HR) were recorded every two minutes for 30 minutes. Vasopressor requirements and side effects were also assessed. Data were analyzed using SPSS v26, with significance p value < 0.05.

Result: Both vasopressors effectively restored SBP without significant differences in efficacy. However, phenylephrine caused a significant HR reduction (particularly at T2–T4 intervals, p value < 0.01), while norepinephrine maintained stable HR. Side effects (e.g., nausea) were minimal and similar between groups. These findings suggest that norepinephrine provides comparable blood pressure control but with better HR stability, potentially improving cardiac output and placental perfusion compared to phenylephrine.

Conclusion: Norepinephrine (4 mcg) and phenylephrine (50 mcg) are equally effective in treating spinal anesthesia-induced hypotension during cesarean sections. However, norepinephrine offers a more favorable hemodynamic profile by avoiding reflex bradycardia, making it a preferable alternative for maternal and fetal well-being.

Keywords: norepinephrine, phenylephrine, spinal anesthesia, hypotension, cesarean section

INTRODUCTION

Cesarean section under spinal anesthesia remains the preferred anesthetic technique in elective deliveries due to its rapid onset and reduced risk of aspiration and fetal exposure to general anesthetics. However, a major complication associated with spinal anesthesia is maternal hypotension, with incidences reported as high as 80–90% due to sympathetic blockade and aortocaval compression by the gravid uterus (Šklebar, Bujas, & Habek, 2019). This condition can significantly reduce uteroplacental perfusion and pose risks to both mother and fetus, necessitating prompt management with vasopressor agents.

Phenylephrine has long been used as a first-line vasopressor in this context. As a pure α1-adrenergic agonist, it causes peripheral vasoconstriction and effectively increases systemic vascular resistance to counteract spinal-induced hypotension. However, its use is frequently accompanied by reflex bradycardia, which may compromise cardiac output and, in turn, fetal oxygenation (Richards, Lopez, & Maani, 2023; Singh et al., 2020). Although effective in blood pressure restoration, the bradycardic effect of phenylephrine has led to increasing interest in alternative vasopressors.

Norepinephrine, a mixed α1- and β1-adrenergic agonist, has been proposed as a more physiologically favorable alternative. Its α1 action provides vasoconstriction, while its β1 component helps maintain heart rate and myocardial contractility, potentially preserving cardiac output more effectively than phenylephrine. Multiple studies have evaluated its utility. For instance, Vallejo et al., (2017) found norepinephrine to be as effective as phenylephrine in preventing hypotension, with improved heart rate preservation. Similarly, Hassani et al., (2018) and Xue et al., (2023)reported in their trials that norepinephrine was associated with fewer incidences of bradycardia and better maternal hemodynamic stability.

Further support comes from recent systematic reviews. Wang, Mao, Liu, Xu, & Yang, (2019) and Xue et al., (2023) concluded that norepinephrine offers a more balanced hemodynamic profile and may be preferable in clinical scenarios requiring sustained cardiac output. Their meta-analyses indicated that norepinephrine and phenylephrine are equally effective in controlling hypotension, but norepinephrine results in fewer episodes of bradycardia and less need for rescue medication.

Despite these encouraging findings, relatively few randomized studies have directly compared fixed bolus doses of norepinephrine and phenylephrine during cesarean section. The current study seeks to address this gap by comparing 4 mcg of norepinephrine to 50 mcg of phenylephrine for the treatment of spinal anesthesia-induced hypotension in cesarean section patients. The objective is to evaluate their comparative effectiveness in blood pressure restoration, heart rate control, and overall safety to inform optimal vasopressor selection in obstetric anesthesia.

METHODS

Study Design

This research adopted a randomized, double-blind clinical trial approach to assess and compare the efficacy of intravenous bolus doses of norepinephrine 4 mcg and phenylephrine 50 mcg in treating hypotension following spinal anesthesia in cesarean section patients. The study was carried out at three healthcare facilities in Medan, Indonesia: Prof. dr. Chairuddin P. Lubis Hospital, Dr. Pirngadi General Hospital, and Haji General Hospital. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara.

Population and Samples

The target population comprised pregnant women between 18 and 40 years old undergoing elective cesarean delivery under spinal anesthesia with an ASA physical status of II. Inclusion criteria required stable baseline hemodynamics and no use of inotropic, chronotropic, or vasoactive drugs preoperatively. Exclusion criteria included emergency procedures, fetal distress, preeclampsia or eclampsia, contraindications to spinal anesthesia, allergic history to the study drugs, and hemodynamic instability. Subjects were excluded if they withdrew, experienced significant clinical deterioration, or did not develop post-spinal hypotension.

Sample size was calculated based on unpaired numerical analysis, resulting in a minimum of 23 participants per group. Subjects were randomly assigned into one of two groups: Group N (norepinephrine 4 mcg) or Group P (phenylephrine 50 mcg), using computerized block randomization via the website www.randomizer.org. The vasopressors were administered intravenously when hypotension occurred, defined as a ≥20% drop in systolic blood pressure from the pre-anesthesia baseline.

Study Instruments

To monitor patient status, non-invasive, calibrated multiparameter monitors were used to assess systolic and diastolic blood pressure, heart rate, and mean arterial pressure. Spinal anesthesia was performed using 10 mg hyperbaric bupivacaine with 25 mcg fentanyl administered intrathecally via a 25G Quincke needle at the L3-L4 interspace. Norepinephrine and phenylephrine solutions were diluted to a concentration of 2 mcg/mL and 25 mcg/mL, respectively, to standardize the 2 mL bolus doses given for each episode of hypotension.

Data Collection

Data were collected starting from baseline (T0), followed by continuous hemodynamic recordings every two minutes for 30 minutes post-spinal anesthesia (T1–T15). The total number of vasopressor administrations and any side effects—such as nausea, bradycardia, vomiting, or shivering—were documented by trained observers blinded to group allocation.

Data Analysis

Statistical analyses were performed using SPSS version 26.0 (IBM). Data normality was assessed using the Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation for normally distributed data, or as medians and ranges otherwise. Inter-group comparisons of continuous data were analyzed using independent samples t-tests or Mann-Whitney U tests as appropriate. Categorical variables were compared using Chi-square tests. A p-value below 0.05 was deemed statistically significant.

RESULTS

Table 1. Patient Characteristics

Characteristics	**Norepinephrine (n: 23)**	**Phenilephrine (n: 23)**	***p-value***
Age (year) (Mean±SD)	30,2 ± 3,8	31,4 ± 2,5	0,33
Gestational Age (week) (Mean±SD)	37,91 ± 1,1	37,78 ± 1,5	0,21
Number of Pregnancies (per time) (Mean±SD)	2,3 ± 0,9	1,95 ± 0,8	0,02

As shown in table 1, This study included 46 parturients scheduled for elective cesarean section under spinal anesthesia who met the inclusion criteria and were randomized equally into two groups: norepinephrine 4 mcg (n = 23) and phenylephrine 50 mcg (n = 23). Baseline demographic data including maternal age, gestational age, and parity were statistically similar between the groups ($p > 0.05$), indicating appropriate comparability for evaluating intervention outcomes.

Table 2. Systolic Pressure Data in the Norepinephrine Group

Time Examination	**Norepinephrine**	***p-value***
T0	122,8 ± 6,3	0,71

T1	92,3 ± 4,9	0,22
T2	114,8 ± 6,9	0,59
T3	117,6 ± 7,5	0,17
T4	117,9 ± 12,4	0,07
T5	123,6 ± 6,6	0,11
T6	123,5 ± 5,2	0,07
T7	123,3 ± 3,8	0,31
T8	122,6 ± 4,6	0,58
T9	123,1 ± 4,9	0,81
T10	121,9 ± 3,3	0,34
T11	120,5 ±2,1	0,28
T12	119,5 ± 2,4	0,50
T13	119,3 ± 1,7	0,06
T14	118,4 ± 1,8	0,06
T15	119,0 ± 2,5	0,08

Table 3. Systolic Pressure Data in the Phenilephrine Group

Time Examination	**Phenilephrine**	***p-value***
T0	123,6 ± 6,8	0,31
T1	96,1 ± 5.9	0,41
T2	118,7 ± 6,7	0,51
T3	122,0 ± 8,2	0,18
T4	123,1 ± 12,2	0,11
T5	128,1 ± 3,7	0,18
T6	125,6 ± 6,5	0,33
T7	123,1 ± 6,8	0,09
T8	122,6 ± 7,5	0,06
T9	123,6 ± 5,3	0,44
T10	122,0 ± 4,9	0,69
T11	117,8 ± 5,4	0,79
T12	116,2 ± 6,8	0,52
T13	109,9 ± 3,8	0,49
T14	112,3 ± 6,9	0,33

T15	113,8 ± 7,1	0,11

Table 4. Effect of Phenilephrine and Ephedrine Administration on Systolic Pressure

Group	Time Examination		*p-value*
	T1	T2	
Norepinephrine	92,3 ± 4,9	114,7 ± 6,9	0,001
Phenilephrine	96,1 ± 5.9	118,7 ± 6,7	0,001

Table 5. Comparison of Systolic Pressure Between Intervention Groups

Time Examination	Norepinephrine	Phenilephrine	*p-value*
T0	122,7 ± 6,3	123,6 ± 6,8	0,49
T1	92,3 ± 4,9	96,1 ± 5.9	0,02
T2	114,7 ± 6,9	118,7 ± 6,7	0,01
T3	117,6 ± 7,5	122,0 ± 8,2	0,06
T4	117,9 ± 12,4	123,1 ±12,2	0,44
T5	123,6 ± 6,6	128,1 ± 3,7	0,11
T6	123,4 ± 5,1	125,6 ± 6,5	0,22
T7	123,2 ± 3,8	123,1 ± 6,8	0,55
T8	122,5 ± 4,6	122,6 ± 7,5	0,44
T9	123,1 ± 4,9	123,6 ± 5,3	0,93
T10	121,9 ± 3,3	122,0 ± 4,9	0,18
T11	120,4 ±2,1	117,8 ± 5,4	0,12
T12	119,5 ± 2,4	116,2 ± 6,8	0,33
T13	119,3 ± 1,7	109,9 ± 3,8	0,43
T14	118,3 ± 1,8	112,3 ± 6,9	0,55
T15	119,1 ± 2,5	113,8 ± 7,1	0,65

Table 6. Difference in Systolic Pressure Between Intervention Groups

Time Examination	Group		*Mean Difference*	P value
T1	Norepinerphine	Phenilephrine	-3.8	0,07
T2	Norepinerphine	Phenilephrine	-4.1	0,11

Hemodynamic parameters were assessed at baseline (T0) and at 2-minute intervals for 30 minutes post spinal anesthesia (T1–T15) (Table 3). Initial systolic blood pressures (SBP) in the norepinephrine and phenylephrine groups were 122.8 ± 6.3 mmHg and 123.6 ± 6.8 mmHg,

respectively. Following the onset of spinal anesthesia, a decrease in SBP was noted in both groups at T1, reaching 92.3 ± 4.9 mmHg in the norepinephrine group and 96.1 ± 5.9 mmHg in the phenylephrine group. A significant increase in SBP was observed at T2 in both groups, with values rising to 114.8 ± 6.9 mmHg and 118.7 ± 6.7 mmHg, respectively (p = 0.01) (Table 4 and 5). The increase confirmed both agents' effectiveness in restoring blood pressure following spinal anesthesia-induced hypotension (Table 6 and 7).

Table 7. Difference in Systolic Pressure Between Intervention Groups

Time Examination	Group		*Mean Difference*	P value
T1	Norepinerphine	Phenilephrine	-3.8	0,07
T2	Norepinerphine	Phenilephrine	-4.1	0,11

The post-hoc analysis revealed a statistically significant difference in SBP at T2 between the norepinephrine and ephedrine groups (mean difference: −5.9 mmHg, p = 0.01) (Table 7). However, the difference between the norepinephrine and phenylephrine groups did not reach statistical significance (mean difference: −4.1 mmHg, p = 0.11), confirming that both norepinephrine and phenylephrine were equally effective in blood pressure recovery.

Table 8. Comparison of Heart Rate in Phenilephrine and Ephedrine Group

Time Examination	Norepinephrine (n : 23)	Phenilephrine (n : 23)	*p-value*
T0	83,0 ± 3,7	81,5 ± 3,5	0,16
T1	91,0 ± 3,8	91,1 ± 3,9	0,94
T2	94,2 ± 3,8	79,6 ± 3,3	0,01
T3	83,7 ± 3,4	70,3 ± 2,61	0,01
T4	85,1 ± 3,3	68,3 ± 2,5	0,01
T5	87,1 ± 4,9	66,7 ± 3,1	0,01
T6	81,3 ± 3,9	69,4 ± 3,1	0,01
T7	80,1 ± 3,9	71,1 ± 3,6	0,01
T8	78,6 ± 3,8	71,8 ± 3,1	0,01
T9	79,5 ± 3,6	76,1 ± 5,1	0,12
T10	79,1 ± 4,1	76,7 ± 3,9	0,22
T11	76,7 ± 2,8	75,6 ± 3,7	0,25
T12	77,1 ±2,1	72,1 ± 4,3	0,35
T13	76,2 ± 1,9	75,2 ± 3,2	0,53
T14	75,1 ± 2,5	76,7 ± 2,5	0,42
T15	76,1 ± 2,8	72,7 ± 1,7	0,44

Heart rate (HR) trends demonstrated more distinct group differences (Table 2). At T2, the HR in the norepinephrine group was 94.2 ± 3.8 bpm compared to 79.6 ± 3.3 bpm in the phenylephrine group (p < 0.01). This discrepancy continued at T3 (83.7 ± 3.4 bpm vs 70.3 ± 2.6 bpm) and T4 (85.1 ± 3.3 bpm vs 68.3 ± 2.5 bpm), confirming a sustained lower HR in the phenylephrine group (p < 0.01). These findings illustrate a significant bradycardic effect of phenylephrine relative to norepinephrine across multiple time points.

Table 9. Comparison of Diastolic Pressure of Phenilephrine and Ephedrine Groups

Time Examination	Norepinephrine (n : 23)	Phenilephrine (n : 23)	P Value
T0	71,4 ± 4,9	74,6 ± 4,6	0,16
T1	62,4 ± 3,8	66,7 ± 6,6	0,94
T2	75,8 ± 3,6	79,3 ± 4,1	0,34
T3	78,5 ± 3,4	81,2 ± 3,8	0,55
T4	77,5 ± 3,2	81,0 ± 3,7	0,41
T5	82,5 ± 6,5	85,1 ± 2,5	0,13
T6	81,6 ± 2,5	78,9 ± 3,4	0,06
T7	79,9 ± 3,3	75,5 ± 3,8	0,07
T8	78,6 ± 3,4	72,9 ± 6,1	0,33
T9	77,3 ± 3,2	74,9 ± 3,4	0,12
T10	77,0 ± 2,1	74,3 ± 3,2	0,22
T11	76,7 ± 1,8	75,7 ± 1,8	0,18
T12	76,8 ± 2,1	76,4 ± 2,1	0,09
T13	75,8 ± 2,7	77,1 ± 2,1	0, 08
T14	76,1 ± 2,2	77,4 ± 2,1	0,17
T15	76,6 ± 2,2	76,6 ± 2,1	0,12

There were no statistically significant differences in diastolic blood pressure (DBP) values between groups at any time point (Table 8). DBP at T0 was 71.4 ± 4.9 mmHg in the norepinephrine group and 74.6 ± 4.6 mmHg in the phenylephrine group, with consistent overlap in all subsequent measurements ($p > 0.05$). This suggests that both vasopressors comparably maintained peripheral vascular resistance necessary to restore DBP during spinal anesthesia-induced hypotension.

Table 10. Side Effects in the Phenilephrine and Ephedrine Group

Side Effect	Intervention Group		*p-value*
	Norepinephrine	Phenilephrine	
Nausea			
Yes	1 (4,3%)	1 (4,3%)	0,76
No	22 (95,7%)	22 (95,7%)	
Vomitting	0	0	
Bradycardia	0	0	
Shivering	0	0	

In the Table 9, Regarding side effects, the most common adverse event was nausea, occurring in one patient (4.3%) in the norepinephrine group and one patient (4.3%) in the phenylephrine group. No cases of vomiting, bradycardia requiring atropine, or shivering were reported in either group. Chi-square analysis confirmed no statistically significant difference in the incidence of nausea between groups ($p = 0.76$), indicating both drugs were well-tolerated.

The need for repeated vasopressor doses was minimal. The average frequency of vasopressor bolus administration was 1.3 ± 0.5 times for norepinephrine and 1.4 ± 0.6 times for phenylephrine,

which did not differ significantly. This reflects the comparably effective pressor response of both agents in preventing recurrent hypotensive episodes. Overall, the primary outcomes of SBP restoration and HR preservation indicate that while norepinephrine and phenylephrine were both effective in correcting hypotension, norepinephrine was superior in preserving maternal HR. The safety profile and incidence of side effects were comparable between the two drugs.

DISCUSSION

This study set out to investigate and compare the clinical performance of norepinephrine and phenylephrine in addressing maternal hypotension triggered by spinal anesthesia during cesarean section. Although both agents were equally effective in restoring blood pressure, norepinephrine provided a clear advantage by maintaining maternal heart rate more effectively, contributing to improved hemodynamic balance.

Phenylephrine acts as a selective α1-adrenergic agonist, promoting vasoconstriction in the arterial and venous systems. This increases systemic vascular resistance, thereby elevating arterial pressure. However, due to the absence of β-adrenergic effects, its rapid and potent vasoconstrictive action often leads to compensatory bradycardia via the baroreceptor reflex. This can diminish cardiac output, a significant concern in obstetric patients (Richards et al., 2023). Phenylephrine's pharmacokinetics include a swift onset and short duration of action, which may necessitate repeated bolus injections or continuous infusion during surgery (Zhang, Qiu, Huang, & Tan, 2024).

Norepinephrine, conversely, has both α1-mediated vasoconstrictive properties and weak β1 agonist effects, allowing it to support myocardial contractility and heart rate. Its pharmacodynamic profile makes it advantageous in maintaining systemic vascular resistance without sacrificing cardiac output. With a similarly rapid onset of action, norepinephrine better preserves cardiovascular stability, especially in scenarios where spinal anesthesia reduces preload and systemic tone (Singh et al., 2020; Wang et al., 2019).

Cardiac output is essential in maintaining uteroplacental blood flow during cesarean section. The combination of vasodilation and reduced venous return following spinal anesthesia impairs preload and systemic vascular resistance. If compounded by bradycardia—as often seen with phenylephrine—cardiac output may decline significantly. Hirose et al., (2019) noted that phenylephrine-induced bradycardia could reduce cerebral oxygenation despite adequate systemic pressure. In contrast, norepinephrine's β1-mediated support allows for greater preservation of cardiac output, thus ensuring sustained perfusion to the placenta and improving fetal oxygen delivery.

Our results are supported by the meta-analysis conducted by Wang et al., (2019), which concluded that norepinephrine offers superior hemodynamic consistency and a lower rate of bradycardia compared to phenylephrine, while being equally effective in counteracting hypotension. Likewise, Singh et al., (2020), using a Bayesian network approach, found that among multiple vasopressors used in neuraxial anesthesia, norepinephrine displayed the most favorable profile regarding maternal safety and cardiovascular stability.

These findings are reinforced by (Sharkey et al., 2019), who observed in a randomized trial that norepinephrine provided more consistent blood pressure control and better heart rate preservation than phenylephrine when administered via bolus. Hassani et al., (2018) similarly reported that norepinephrine infusions were associated with fewer cardiovascular fluctuations and less frequent bradycardia episodes. Despite its established effectiveness, phenylephrine's side effect of reducing

heart rate may be problematic in certain clinical scenarios, particularly in patients with preexisting bradycardia or cardiac compromise. The requirement for adjunctive drugs such as atropine adds complexity to intraoperative management. On the other hand, norepinephrine's more balanced adrenergic effects result in fewer instances of reflex bradycardia and more stable cardiovascular responses throughout surgery.

One of the strengths of this study lies in its design—a double-blinded, randomized trial with standardized dosing of each agent, allowing direct and unbiased comparison. The consistent monitoring of hemodynamic variables also provided robust and clinically relevant insights into each vasopressor's profile. Nevertheless, the study is not without limitations. Firstly, cardiac output was not directly measured, and conclusions on its preservation were inferred from trends in heart rate. Including tools such as Doppler ultrasonography or non-invasive cardiac output monitors would have yielded more definitive data. Secondly, the absence of neonatal outcome measures, such as Apgar scores or umbilical cord blood gases, limited assessment of the downstream effects of improved maternal perfusion. Additionally, the trial focused solely on bolus administration, leaving unanswered questions about the comparative performance of these drugs when given via continuous infusion—a method gaining popularity in clinical anesthesia. Lastly, although adequately powered, the relatively small sample size restricts generalizability and may not capture less common adverse events.

In terms of clinical implications, these findings contribute to a growing trend in obstetric anesthesia practice that favors norepinephrine over phenylephrine as the first-line vasopressor. As evidence accumulates regarding its balanced adrenergic action and reduced risk of bradycardia, more guidelines are recommending norepinephrine, particularly in cases where maintaining cardiac output is essential. Its practicality in bolus or infusion form and the consistency of its hemodynamic effects make it a promising agent for routine use in cesarean delivery.

In summary, this study validates the use of norepinephrine 4 mcg and phenylephrine 50 mcg as equally effective interventions for spinal anesthesia-induced hypotension. However, norepinephrine offers superior heart rate preservation, potentially improving maternal cardiac output and uteroplacental circulation. These results are consistent with a broad array of literature and suggest that norepinephrine should be strongly considered as a primary vasopressor choice in cesarean section anesthesia. Future research should involve larger populations, include direct cardiac output and fetal outcome assessments, and examine continuous administration regimens to establish optimal protocols.

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CONCLUSION

This clinical trial confirmed that intravenous bolus doses of 4 mcg norepinephrine and 50 mcg phenylephrine are both effective in correcting hypotension resulting from spinal anesthesia during cesarean delivery. Both drugs successfully restored maternal blood pressure with similar efficacy and were associated with a low incidence of side effects. However, norepinephrine was notably more effective in maintaining heart rate stability, in contrast to the significant bradycardia observed with phenylephrine. This characteristic is particularly advantageous in obstetric settings, where sustained maternal cardiac output is vital for ensuring adequate uteroplacental circulation. Therefore, norepinephrine offers a more balanced hemodynamic profile and may serve as a preferable option over phenylephrine when heart rate preservation is clinically desirable. These findings support a shift toward incorporating norepinephrine as a primary vasopressor in obstetric anesthetic practice and

suggest further investigation into its impact on neonatal outcomes to strengthen clinical recommendations.

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