

Comparison of The Efficacy of Intravenous Norepinephrine and Phenylephrine as Vasopressor Agents in The Management of Septic Shock in ICU Patients at Haji Adam Malik General Hospital Using Lactate and Stroke Volume Variation Indicators

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ABSTRACT

Background: Septic shock is a life-threatening complication of sepsis, characterized by refractory hypotension and tissue hypoperfusion, requiring rapid vasopressor therapy. Norepinephrine is the drug of choice, but phenylephrine is still used in certain conditions, such as tachyarrhythmia or high output. Evidence comparing the effectiveness of the two is still limited, especially in Indonesian ICUs. Therefore, this study assessed the efficacy of norepinephrine and phenylephrine using lactate clearance and stroke volume variation (SVV) as indicators of perfusion and hemodynamic response in the intensive care unit (ICU) of Haji Adam Malik General Hospital, Medan.

Methods: This study was a prospective, double-blind, randomized controlled clinical trial conducted in the ICU of Haji Adam Malik General Hospital, Medan, involving 32 adult patients (aged 18–65 years) with septic shock, as defined by the Sepsis-3 criteria. Patients were randomly assigned to two groups receiving norepinephrine infusion (n = 16) or phenylephrine infusion (n = 16) as the primary vasopressor. Lactate levels and SVV were measured at baseline (T0) and 6 hours after therapy (T1). The primary outcome was the change in lactate and SVV, with analysis using paired and independent t-tests at a significance level of $p < 0.05$.

Results: 32 patients were divided into two groups, each with 16 patients receiving norepinephrine or phenylephrine. After 6 hours of therapy, norepinephrine reduced lactate levels from 8.41 ± 1.88 to 5.76 ± 1.99 mmol/L and SVV from 14.25 ± 2.17 to 8.18 ± 1.90 mmHg ($p < 0.001$). Phenylephrine also reduced lactate from 7.40 ± 1.77 to 6.70 ± 1.77 mmol/L and SVV from 15.93 ± 2.56 to 12.50 ± 2.63 mmHg ($p < 0.001$).

Conclusions: Intravenous norepinephrine is more effective than phenylephrine in lowering lactate and improving SVV in septic shock patients in the ICU, thus supporting its use as the primary vasopressor. Phenylephrine remains an alternative with close hemodynamic monitoring. Further studies are needed to confirm these findings and understand the mechanism behind the difference in effectiveness between the two.

Keywords: lactate levels; norepinephrine; phenylephrine; septic shock; stroke volume variation

INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.¹ Septic shock represents the most severe form of sepsis, characterized by persistent hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) ≥ 65 mmHg and associated with elevated lactate levels (> 4 mmol/L) despite adequate fluid resuscitation.^{2,3}

Each year, 750,000 patients in the United States experience sepsis, which is the leading cause of death among critically ill patients, claiming more than 210,000 lives annually. The annual incidence rate of severe sepsis and septic shock in the United States reaches 300 cases per 100,000 people. Approximately 15% of sepsis patients experience septic shock, and about 10% of all patients with septic shock are admitted to intensive care units (ICUs) and have a mortality rate exceeding 50%.^{1,4} Epidemiological data from Asia in 2009, collected from 150 ICUs across 16 countries, including Indonesia, reported that sepsis and septic shock accounted for 10.9% of ICU cases, with a mortality rate of 44.5%.⁵ In Indonesia, a local hospital-based report documented 233 cases of sepsis at Haji Adam Malik General Hospital, Medan, in 2015.⁶

Given the low complication rate of peripheral vasopressors and the possibility of faster blood pressure restoration, the benefit of initiating vasopressors for a short duration via a vein near the antecubital fossa may outweigh the risks. Therefore, the 2021 Surviving Sepsis Campaign (SSC) issued a weak recommendation in support of rapidly initiating peripheral vasopressors. If vasopressor infusion is still required after a short period, it should be infused via central venous access as soon as

possible and, if resources are available, to minimize the risk of complications.³

Although there is some evidence that early vasopressor initiation may be preferred over delayed initiation (i.e., after complete fluid resuscitation), there remains debate on whether vasopressors should be administered simultaneously with fluid infusion or slightly later. A retrospective analysis of 2,849 patients with septic shock suggests starting vasopressor agents, specifically norepinephrine in this case, at least 1 hour after initiating fluid infusion.⁷

Several types of vasopressor agents are available, such as norepinephrine and phenylephrine. Norepinephrine is the first-line vasopressor for managing septic shock, and it is the most suitable for maintaining MAP by increasing systemic vascular resistance after or during proper fluid resuscitation. Norepinephrine is derived from tyrosine and acts as a peripheral vasoconstrictor (activating α -adrenergic receptors), stimulates the strength of heart contraction, and dilates coronary arteries (activating β -adrenergic receptors).⁷⁻¹²

Phenylephrine is another vasopressor that can be used in septic shock management. Phenylephrine is an alpha-1 adrenergic receptor agonist with minimal to no beta-adrenergic activity. Phenylephrine increases MAP by inducing vasoconstriction in veins and arteries and increasing cardiac preload without significantly affecting myocardial cells. However, with the introduction of the SSC, sepsis management has undergone numerous changes, leading to the development of a more standardized approach to septic shock. Norepinephrine is now the vasopressor and inotrope of choice in this context.^{13,14}

A pilot study comparing phenylephrine and norepinephrine in regional and systemic hemodynamic improvement during the early phase of septic shock showed favorable results. When administered as a first-line vasopressor, phenylephrine effectively increased MAP without impairing gastrointestinal and hepatosplanchic perfusion compared to norepinephrine.¹⁵

A recent study conducted by Lisa *et al.* on septic shock patients administered with phenylephrine or norepinephrine showed no difference in 28-day mortality between the two groups. Further analysis of high-risk patients (age >70 years, history of heart disease) also showed no significant difference between the two agents.¹⁵

Another study also showed that phenylephrine can match norepinephrine in improving abnormal hemodynamics and metabolism in sepsis patients, with the added benefit that phenylephrine can decrease heart rate (HR) and increase stroke volume index.¹⁵

The success of septic shock management can be assessed by the patient's lactate levels and hemodynamic conditions. Lactate is a cellular metabolic product that may accumulate when cells lack oxygen (hypoxia). Lactate serves as a biochemical marker for critical illness, trauma, and sepsis. High lactate levels indicate global tissue hypoxia, increased glycolysis, endotoxin effects, and anaerobic metabolism markers. Hypoxic conditions are characterized by elevated lactate levels, leading to a worse prognosis.¹⁵

In a study conducted by Nygren *et al.*, norepinephrine and phenylephrine were compared in terms of increasing MAP by up to 30%. The results showed that

phenylephrine administration was associated with a significant increase in splanchnic oxygen extraction and mixed venous to hepatic venous oxygen saturation gradient compared to norepinephrine, despite similar cardiovascular variables. These findings indicate that phenylephrine induces more pronounced global splanchnic vasoconstriction.¹⁶

The patient's hemodynamic status is critical for assessing treatment response. SVV is one of the hemodynamic indicators with higher sensitivity and specificity compared to other commonly used parameters, including HR, MAP, central venous pressure (CVP), and pulmonary artery occlusion pressure (PAOP). SVV is not a direct indicator of preload but reflects the relative preload responsiveness. This parameter can help determine fluid responsiveness, particularly in patients with hemodynamic instability, such as those experiencing septic shock.¹⁶

Early norepinephrine administration significantly reduces SVV, even with a low tidal volume. Such findings can be attributed to the α -adrenergic-mediated effect, which reduces systemic venous capacitance. On the other hand, phenylephrine increases ventricular filling time due to its heart rate-lowering and diastolic extension effects. This means that phenylephrine increases preload, thereby reducing SVV.¹⁶

Based on the above background, this study aimed to evaluate the effectiveness of norepinephrine and phenylephrine vasopressor agents in the management of septic shock, using lactate levels and SVV as assessment indicators in patients at Haji Adam Malik General Hospital, Medan.

METHODS

This study was a double-blind, parallel-group randomized controlled trial conducted in the ICU of Haji Adam Malik General Hospital, Medan.

Eligible participants were adults aged 18–65 years with septic shock as supported by sequential organ failure assessment (SOFA) criteria, receiving mechanical ventilation, and co-managed by the Department of Anesthesiology and Intensive Therapy. Exclusion criteria included absence of consent from patients or surrogates, liver dysfunction indicated by serum SGOT and/or SGPT > 50 U/L, and hemoglobin < 8 g/dL.

Participants were randomly allocated in a 1:1 ratio to norepinephrine or phenylephrine. Allocation was concealed, and treating clinicians, bedside assessors, and data analysts were blinded to group assignment.

Participants received either norepinephrine or phenylephrine infusion as the primary vasopressor according to unit protocols. Lactate concentration and SVV were measured at baseline (T0) and after 6 hours of therapy (T1).

Primary outcomes were changes from T0 to T1 in lactate concentration and SVV. Secondary outcomes were changes in systolic blood pressure (SBP) and HR over the same interval.

The required sample size was calculated for an unpaired two-sample comparison of means using lactate as the efficacy variable with $\alpha=0.05$, power=80% ($\beta=0.20$), an expected mean difference (Δ) of 0.85 mmol/L, and a pooled standard deviation of 1.496. The computation yielded 13.8 participants

per arm; allowance for $\approx 10\%$ attrition increased the target to 16 per arm (total n=32).

Data were analyzed using SPSS version 26. Continuous variables were summarized as mean \pm SD when normally distributed or median (IQR) when non-normal. Normality was assessed with the Shapiro–Wilk test and homogeneity of variances with Levene's test. Within-group pre–post comparisons used paired t-tests for normal data or Wilcoxon signed-rank tests for non-normal data. Between-group comparisons at T0 and T1 used independent t-tests for normal data or Mann–Whitney U tests for non-normal data. Categorical variables were compared with the chi-square test or Fisher's exact test, as appropriate. The significance threshold was set at $p<0.05$. All results were reported with corresponding 95% confidence intervals (CI) to indicate the precision of the estimates. Analyses followed the randomized groups.

RESULTS

Table 1 summarizes the demographic and clinical characteristics of the participants. Baseline demographic and clinical characteristics were comparable between groups, with no statistically significant differences in age, sex distribution, body mass index (BMI), qSOFA score, SBP, or HR ($p > 0.05$). Both groups represented a high-risk septic shock population, indicated by a median qSOFA of 3. This balance supports the validity of subsequent between-group comparisons.

Table 2 summarizes the hemodynamic changes after 6 hours of norepinephrine administration. In the norepinephrine group, lactate and SVV decreased significantly after 6 hours, while SBP

and HR increased (all $p < 0.05$). These findings indicate improved perfusion and hemodynamic stability, consistent with norepinephrine's combined α - and β -adrenergic effects that enhance vascular tone and cardiac output.

Table 3 presents the comparison of lactate levels measured before and after administering Phenylephrine for 6 hours. In the phenylephrine group, lactate and SVV also decreased significantly, and SBP increased (all $p < 0.05$). However, HR decreased, consistent with reflex bradycardia due to selective α -adrenergic activity. This suggests phenylephrine improves perfusion, but its effect is less pronounced compared to norepinephrine.

Between-group comparison of lactate levels showed no baseline difference ($p = 0.130$). After 6 hours, both groups achieved significant reductions, but the mean reduction was greater with norepinephrine ($\Delta 2.65 \pm 0.82$ vs. $\Delta 0.70 \pm 0.27$; $p = 0.001$). This demonstrates norepinephrine's superior efficacy in enhancing lactate clearance as a marker of tissue perfusion. (Table 4)

Similarly, SVV did not differ at baseline ($p = 0.054$), but norepinephrine achieved a larger median reduction compared with phenylephrine (6 [4–11] vs. 3 [1–8]; $p = 0.001$). These results highlight norepinephrine's greater effect on optimizing preload responsiveness and overall hemodynamic stability. (Table 5)

Table 1. Sample characteristics

Parameter	Norepinephrine	Phenylephrine	p-value
N (M/F)	16 (8/8)	16(9/7)	0.723 ^c
Age (years) ^a	54.25 \pm 18.89	54.06 \pm 14.61	0.975 ^d
Body weight (kg) ^a	52.12 \pm 8.58	50 \pm 12.85	0.586 ^d
Body height (cm) ^a	160.37 \pm 7.50	159.93 \pm 11.96	0.902 ^d
Body mass index (BMI; kg/m ²) ^a	20.14 \pm 2.14	19.17 \pm 2.76	0.278 ^d
Qsofa score ^b	3 (2 – 3)	3 (2 – 3)	1.000 ^e
Systolic blood pressure (SBP)	76.31 \pm 9.49	73.31 \pm 6.03	0.295 ^d
Heart rate (HR)	82.31 \pm 10.24	86.75 \pm 8.28	0.188 ^d

^aNormally distributed data (mean \pm SD (standard deviation)); ^bAbnormally distributed data (median (min-max)); ^cChi-Square test; ^dT-independent test; ^eMann-Whitney test

Table 2. Comparison of lactate levels, SVV, SBP, and HR before and after norepinephrine administration

Parameter	T0	T1	p-value	CI
Lactate levels (mmol/L)	8.41 \pm 1.88	5.76 \pm 1.99	0.001*	1.19 to 4.11
Stroke volume variation (SVV)	14.25 \pm 2.17	8.18 \pm 1.90	0.001*	4.53 to 7.61
Systolic blood pressure (SBP)	76.31 \pm 9.49	122.06 \pm 12.99	0.001*	-54.32 to -37.18
Heart rate (HR)	82.31 \pm 10.24	106.62 \pm 10.93	0.001*	-32.29 to -16.33

*Statistically significant findings based on the paired-T test

Table 3. Comparison of lactate levels, SVV, SBP, and HR before and after phenylephrine administration

Parameter	T0	T1	p-value	CI
Lactate levels (mmol/L)	7.40 ± 1.77	6.70 ± 1.77	0.001*	-0.63 to 2.03
Stroke volume variation (SVV)	15.93 ± 2.56	12.50 ± 2.63	0.001*	1.47 to 5.39
Systolic blood pressure (SBP)	73.31 ± 6.03	95.5 ± 13.29	0.001*	-29.97 to -14.41
Heart rate (HR)	86.75 ± 8.28	81.75 ± 8.69	0.001*	-1.40 to 11.40

*Statistically significant findings based on paired-T test

Table 4. Comparison of lactate levels for norepinephrine and phenylephrine administration.

Parameter (Lactate levels; mmol/L)	T0	T1	p-value	CI
Lactate levels T0	8.41 ± 1.88	7.40 ± 1.77	0.130	-0.31 to 2.33
Lactate levels T1	5.76 ± 1.99	6.70 ± 1.77	0.170	-2.30 to 0.42
Δ of lactate levels	2.65 ± 0.82	0.70 ± 0.27	0.001*	1.51 to 2.39

*Statistically significant findings based on paired-T test

Table 5. Comparison of SVV for norepinephrine and phenylephrine administration.

Parameter (Lactate levels; mmol/L)	T0	T1	p-value
SVV T0	14.25 ± 2.17	15.93 ± 2.56	0.054
SVV T1	8.18 ± 1.90	12.50 ± 2.63	0.001*
Δ of SVV	6 (4 – 11)	3 (1 – 8)	0.001**

*Statistically significant findings based on paired-T test; **Statistically significant findings based on Mann-Whitney test

DISCUSSION

Sepsis and septic shock remain among the leading causes of mortality in critically ill patients, presenting a major challenge in intensive care management. Vasopressors are central to therapy, with norepinephrine established as the first-line agent and phenylephrine occasionally considered in selected clinical contexts.¹

Both groups in this trial were comparable at baseline, with no significant differences in demographic or clinical variables, which supports the validity of the observed outcomes.

Norepinephrine administration resulted in significant reductions in lactate and SVV, accompanied by increases in SBP and HR, indicating improved tissue perfusion and hemodynamic stability. These effects are attributable to the combined α -adrenergic vasoconstrictive

and β_1 -adrenergic inotropic activity of NE, which simultaneously enhances vascular tone and cardiac output.¹⁰ Phenylephrine also improved lactate and SVV and increased SBP, but was associated with a reduction in HR, consistent with its selective α -adrenergic activity and absence of β -adrenergic support.^{15,16}

Direct comparisons demonstrated that norepinephrine produced greater lactate clearance and SVV reduction than phenylephrine, confirming its superior efficacy in optimizing both macrocirculatory and microcirculatory parameters. These findings are consistent with prior studies reporting that norepinephrine is more effective in improving global perfusion, whereas phenylephrine may induce more pronounced splanchnic vasoconstriction and potentially compromise regional oxygen delivery.¹⁴

From a clinical perspective, the results reinforce the Surviving Sepsis Campaign (SSC) guideline recommending norepinephrine as the vasopressor of choice in septic shock.³ Phenylephrine may be considered in specific scenarios, such as in patients with tachyarrhythmias or contraindications to β -adrenergic stimulation, but its use should be carefully individualized.¹⁴ Optimal management requires invasive monitoring: arterial catheters enable continuous MAP and SVV assessment, serial lactate measurements provide biochemical markers of perfusion, and central venous access allows for secure vasopressor delivery and monitoring of central venous oxygen saturation.¹⁴⁻¹⁶

The superior performance of norepinephrine in reducing lactate reflects improved global oxygen delivery and reduced anaerobic metabolism.⁸ Its dual adrenergic effects restore perfusion pressure while augmenting cardiac output, which explains the greater SVV reduction and faster hemodynamic stabilization. In contrast, phenylephrine acts solely through α -adrenergic pathways, raising systemic vascular resistance without enhancing contractility. This pharmacologic profile may explain why phenylephrine was less effective in improving markers of perfusion.^{14,15,16}

This study has limitations, including its single-center setting and relatively small sample size, which may limit generalizability. Potential confounding factors, such as variations in adjunctive therapy and clinical management, could also have influenced outcomes. The study was designed as a randomized controlled trial; however, the endpoints were restricted to short-term hemodynamic parameters (lactate and stroke volume variation). Longer-term

outcomes such as 28-day mortality, ICU length of stay, and organ dysfunction scores were not assessed. Further multicenter RCTs with larger cohorts and extended follow-up are warranted to validate these findings and provide more comprehensive clinical endpoints.

CONCLUSION

Norepinephrine demonstrated greater effectiveness than phenylephrine in reducing lactate levels and SVV in patients with septic shock, indicating superior improvement in tissue perfusion and hemodynamic stability. These findings support norepinephrine as the preferred vasopressor in this setting, while phenylephrine may be considered in selected cases. The conclusions are limited by the single-center design and small sample size, and further multicenter trials with larger cohorts and long-term outcomes are needed to confirm these results.

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