Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 15 [7] June 2026. 51-55

Online ISSN 2277-1808
Journal's URL: http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Comparison of Norepinephrine Alone versus Norepinephrine plus Vasopressin in Refractory Septic Shock: A Prospective Study

Muhammad Usama Atta[1], Zainab Mustafa[2], M. Rizwan Ishaque[3], Nida Ayesha[4], Asma Shaukat[5], Obaid Anwar[6]

1. Central Park Medical College, Lahore, Pakistan.
2. Demonstrator, Department of Pharmacology, King Edward Medical University (KEMU), Lahore, Pakistan.
3. Assistant Professor, Medicine, Sahiwal Medical College, Sahiwal, Pakistan.
4. Assistant Professor, Department of Pharmacology, Jinnah Sindh Medical University, Karachi, Pakistan.
5. Professor of Pharmacology, Women Medical College, Abbottabad, Pakistan.
6. Assistant Professor, Pharmacology, Independent Medical College, Faisalabad, Pakistan.

Muhammad Usama Atta: Corresponding author
Orchid id: 0009-0008-8837-2488

ABSTRACT

Refractory septic shock remains a critical condition associated with high mortality despite adequate fluid resuscitation and norepinephrine therapy. Vasopressin has been proposed as an adjunct vasopressor to improve hemodynamic stability and reduce catecholamine requirements. The present study aimed to compare the efficacy and clinical outcomes of norepinephrine alone versus norepinephrine plus vasopressin in patients with refractory septic shock. A prospective comparative study was conducted on 180 patients diagnosed with septic shock requiring vasopressor support. Patients were divided into two equal groups: norepinephrine alone (n=90) and norepinephrine plus vasopressin (n=90). Primary outcomes included mean arterial pressure (MAP), time to hemodynamic stability, and vasopressor dose requirements. Secondary outcomes included lactate clearance, urine output, acute kidney injury incidence, and 28-day mortality. The combination therapy group demonstrated significantly higher MAP at 6 and 24 hours (p<0.001), reduced norepinephrine requirements (p<0.001), improved lactate clearance (p<0.001), and higher urine output (p=0.002). The 28-day mortality was significantly lower in the combination group (34.4% vs 48.9%, p=0.048). ICU length of stay was also reduced. The addition of vasopressin to norepinephrine improves hemodynamic stability and reduces mortality in refractory septic shock. This combination may provide superior vasopressor support compared to norepinephrine monotherapy.

Keywords: *Septic shock, norepinephrine, vasopressin, vasopressors*

Received 18.05.2026 Revised 27.05.2026 Accepted 08.06.2026

INTRODUCTION

Septic shock represents the most severe manifestation of sepsis and is characterized by profound circulatory, cellular, and metabolic abnormalities associated with a high risk of mortality. Despite advances in critical care management, septic shock continues to contribute significantly to intensive care unit (ICU) admissions and mortality worldwide. The pathophysiology involves dysregulated host responses to infection, leading to widespread vasodilation, capillary leakage, and impaired tissue perfusion, ultimately resulting in multiorgan dysfunction.[1-3]

The cornerstone of septic shock management includes early fluid resuscitation, prompt antimicrobial therapy, and vasopressor support to restore adequate mean arterial pressure (MAP). Norepinephrine remains the first-line vasopressor due to its potent α-adrenergic vasoconstrictive effects with limited chronotropic activity. However, a subset of patients develops refractory septic shock, defined as persistent hypotension despite adequate fluid resuscitation and escalating doses of norepinephrine.

In such cases, reliance on high-dose catecholamines may be associated with adverse effects including tachyarrhythmias, increased myocardial oxygen consumption, immunomodulatory suppression, and peripheral ischemia. This has led to increased interest in adjunct vasopressor therapy aimed at restoring vascular tone through alternative pathways.[4-7]

Vasopressin, an endogenous antidiuretic hormone, acts on V1 receptors in vascular smooth muscle, leading to vasoconstriction independent of adrenergic receptors. In septic shock, relative vasopressin deficiency has been documented, particularly in prolonged and severe cases, suggesting a physiological rationale for exogenous supplementation. The use of vasopressin as an adjunct to norepinephrine may improve vascular responsiveness, reduce catecholamine requirements, and enhance hemodynamic stability.[8-10]

Previous clinical studies have demonstrated variable results regarding the survival benefit of vasopressin in septic shock. While some trials have shown reduced vasopressor requirements and improved renal perfusion, others have failed to demonstrate a significant mortality benefit. This inconsistency highlights the need for further prospective evaluation, particularly in patients with refractory shock requiring high-dose vasopressor support.

Another important consideration is the impact of vasopressor choice on organ function. Excessive norepinephrine exposure has been associated with renal vasoconstriction and impaired microcirculation. Vasopressin, in contrast, may preferentially redistribute blood flow and improve glomerular filtration pressure, potentially reducing the incidence of acute kidney injury. However, concerns remain regarding ischemic complications at higher doses.

In recent years, combination vasopressor therapy has gained attention as a strategy to optimize hemodynamic support while minimizing catecholamine toxicity. The Surviving Sepsis Campaign guidelines recommend the addition of vasopressin at low fixed doses in patients requiring escalating norepinephrine doses, although the level of evidence supporting this recommendation remains moderate.

Despite these recommendations, real-world practice varies considerably, and there remains uncertainty regarding the magnitude of benefit provided by combination therapy in refractory septic shock. Moreover, data from prospective comparative studies remain limited, particularly in resource-constrained critical care settings.

The present study was therefore designed to compare norepinephrine monotherapy with norepinephrine plus vasopressin in patients with refractory septic shock. The study specifically evaluated hemodynamic parameters, vasopressor requirements, organ perfusion markers, and clinical outcomes including mortality and ICU length of stay. By directly comparing these two strategies in a controlled prospective design, this study aims to provide clinically relevant evidence to guide vasopressor selection in critically ill patients.

MATERIAL AND METHODS

A prospective comparative study was conducted in the intensive care unit of Central Park Medical College, Lahore, Pakistan a tertiary care hospital over a 12-month period. Adult patients aged 18–75 years diagnosed with septic shock requiring vasopressor support were included. Septic shock was defined according to Sepsis-3 criteria as sepsis with persistent hypotension requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate >2 mmol/L despite adequate fluid resuscitation.

A total of 180 patients meeting inclusion criteria were enrolled and allocated into two equal groups. Group A received norepinephrine alone, while Group B received norepinephrine plus vasopressin infusion at a fixed dose of 0.03 units/min in addition to norepinephrine. Allocation was performed using a computer-generated randomization sequence.

Sample size was calculated using OpenEpi software assuming a mortality difference of 20% between groups, 95% confidence interval, 80% power, and equal allocation ratio, yielding a minimum required sample size of 164 patients. To compensate for dropouts, the sample size was increased to 180 patients.

Inclusion criteria included patients with confirmed septic shock requiring vasopressor support after adequate fluid resuscitation. Exclusion criteria included age below 18 years, pregnancy, chronic liver failure, end-stage renal disease on dialysis, pre-existing severe heart failure (EF <30%), and prior vasopressin therapy before ICU admission.

Baseline demographic data including age, sex, source of infection, APACHE II score, and SOFA score were recorded. Hemodynamic parameters including MAP, heart rate, norepinephrine dose, urine output, and serum lactate levels were measured at baseline, 6 hours, 24 hours, and 48 hours.

Primary outcomes included achievement of target MAP, total norepinephrine dose requirement, and time to hemodynamic stability. Secondary outcomes included lactate clearance, incidence of acute kidney injury (defined by KDIGO criteria), ICU length of stay, and 28-day mortality.

All patients received standard sepsis management according to current guidelines including antibiotics, fluid resuscitation, and supportive care. Vasopressor titration was performed by intensive care physicians blinded to study outcomes.

Data analysis was performed using SPSS version 26. Continuous variables were expressed as mean ± standard deviation and compared using independent t-test. Categorical variables were analyzed using chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 180 patients with refractory septic shock were included and equally divided into two groups: norepinephrine alone (Group A, n=90) and norepinephrine plus vasopressin (Group B, n=90). Baseline characteristics were comparable between groups.

Table 1. Baseline demographic and clinical characteristics

Variable	NE alone (n=90)	NE + Vasopressin (n=90)	p-value
Age (years)	58.4 ± 12.6	59.1 ± 11.9	0.712
Male, n (%)	52 (57.8)	54 (60.0)	0.765
APACHE II score	24.8 ± 5.2	25.1 ± 5.6	0.684
SOFA score	10.6 ± 2.3	10.9 ± 2.5	0.498
Source of infection (pneumonia %)	46.7%	48.9%	0.771

Interpretation: Both groups were comparable at baseline with no statistically significant differences, ensuring homogeneity for outcome comparison.

Table 2. Hemodynamic and perfusion parameters

Parameter	NE alone	NE + Vasopressin	p-value
MAP at 6 hours (mmHg)	63.2 ± 6.8	71.5 ± 7.1	<0.001
MAP at 24 hours (mmHg)	68.4 ± 7.2	76.9 ± 6.5	<0.001
Norepinephrine dose (µg/kg/min)	0.32 ± 0.08	0.21 ± 0.06	<0.001
Lactate at 24h (mmol/L)	3.9 ± 1.2	2.6 ± 0.9	<0.001
Lactate clearance (%)	32.1 ± 10.4	48.7 ± 11.2	<0.001

Interpretation: Combination therapy significantly improved MAP, reduced vasopressor requirement, and enhanced lactate clearance.

Table 3. Clinical outcomes

Outcome	NE alone	NE + Vasopressin	p-value
AKI incidence (%)	44 (48.9%)	30 (33.3%)	0.028
Urine output (mL/day)	1020 ± 340	1345 ± 410	0.002
ICU length of stay (days)	12.6 ± 4.3	9.8 ± 3.7	0.001
28-day mortality (%)	44 (48.9%)	31 (34.4%)	0.048

Interpretation: Combination therapy significantly reduced AKI incidence, ICU stay, and mortality.

DISCUSSION

The present study demonstrates that the addition of vasopressin to norepinephrine significantly improves hemodynamic stability in patients with refractory septic shock. The observed increase in mean arterial pressure at both early and later time points suggests a synergistic vasopressor effect. This finding aligns with the physiological role of vasopressin in restoring vascular tone in vasodilatory shock states.

A key observation was the substantial reduction in norepinephrine dose requirements in the combination group. Excessive catecholamine exposure is associated with adverse cardiovascular and metabolic effects, including arrhythmias and impaired microcirculation. By reducing norepinephrine dependency, vasopressin may mitigate these harmful effects while maintaining adequate perfusion pressure.

Lactate clearance was significantly improved in patients receiving combination therapy, indicating better tissue perfusion and oxygen utilization. Serum lactate is a well-established marker of shock severity and prognostic indicator in septic patients. Improved clearance suggests enhanced reversal of tissue hypoperfusion in the vasopressin group.

Renal outcomes also demonstrated significant benefit, with lower incidence of acute kidney injury and higher urine output in the combination therapy group. These findings support the hypothesis that vasopressin may improve renal perfusion through preferential efferent arteriolar constriction and redistribution of renal blood flow, although this mechanism remains partially debated in recent literature [11–13]

The hemodynamic improvements observed in this study are consistent with the pathophysiology of septic shock, which involves profound vasodilation due to inflammatory mediator release, endothelial dysfunction, and reduced catecholamine responsiveness. Progressive depletion of endogenous vasopressin leads to relative deficiency, and exogenous supplementation restores vascular tone via V1 receptor–mediated vasoconstriction, independent of adrenergic pathways. This complementary mechanism likely explains the superior blood pressure control seen with combination therapy and supports a multimodal vasopressor approach.

Importantly, vasopressin may also enhance microcirculatory function. In septic shock, normalization of systemic blood pressure does not guarantee adequate tissue perfusion due to microvascular dysfunction. Improved lactate clearance in this study suggests better tissue perfusion, possibly through optimized blood

flow redistribution and preserved perfusion of vital organs. These findings emphasize the need to assess both hemodynamic and metabolic parameters in evaluating treatment efficacy.

The renal protective effects are clinically relevant, as acute kidney injury is a major complication of septic shock. Reduced incidence of AKI and improved urine output with vasopressin may reflect better renal perfusion and maintenance of glomerular filtration, potentially through efferent arteriolar constriction. Stabilization of systemic hemodynamics may further reduce ischemic injury and support renal recovery.

The observed reduction in mortality may be attributed to rapid hemodynamic stabilization, improved organ perfusion, and reduced catecholamine exposure, thereby minimizing associated adverse effects such as arrhythmias and increased myocardial oxygen demand. However, given the multifactorial nature of septic shock outcomes, these findings should be interpreted cautiously.

Clinically, the results suggest that earlier addition of vasopressin in patients inadequately responsive to norepinephrine may improve outcomes and reduce ICU stay. Nevertheless, due to heterogeneity in patient response and treatment variables, larger multicenter trials are required to confirm these findings and establish optimal therapeutic strategies.

Mortality reduction observed in the combination group highlights the potential clinical advantage of early adjunct vasopressor therapy in refractory septic shock. While previous large trials have shown mixed results regarding mortality benefit, the present study suggests that selected patients with high vasopressor requirements may derive survival benefit from vasopressin addition [14–16].

The reduction in ICU length of stay further supports improved clinical recovery in patients receiving combination therapy. Faster hemodynamic stabilization likely contributes to earlier organ recovery, reduced ventilator dependency, and decreased ICU resource utilization. This finding is particularly relevant in high-burden critical care environments.

Overall, the results support the integration of vasopressin as an early adjunct in refractory septic shock rather than a late rescue therapy. The physiological rationale, combined with observed improvements in perfusion and outcomes, suggests that dual vasopressor therapy provides superior hemodynamic support compared to norepinephrine alone [17–19].

In conclusion, the present study adds to the growing body of evidence supporting the use of vasopressin as an adjunctive vasopressor in refractory septic shock. The combination of vasopressin and norepinephrine was associated with improved hemodynamic stability, enhanced lactate clearance, reduced norepinephrine requirements, better renal outcomes, shorter ICU stay, and lower mortality compared with norepinephrine alone. These findings highlight the potential value of a multimodal vasopressor strategy that targets different physiological pathways involved in septic shock. As understanding of shock pathophysiology continues to evolve, early adjunctive vasopressin therapy may become an increasingly important component of individualized hemodynamic management in critically ill septic patients.

CONCLUSION

The addition of vasopressin to norepinephrine significantly improves hemodynamic stability, lactate clearance, and renal outcomes in refractory septic shock. Combination therapy is associated with reduced vasopressor requirements and lower 28-day mortality. Early use of vasopressin as adjunct therapy may offer superior clinical benefit compared to norepinephrine monotherapy.

REFERENCES.

1. Evans L., Rhodes A., Alhazzani W., Antonelli M., Coopersmith C.M., French C., Machado F.R., et al. (2021). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Intensive Care Medicine. 47:1181–1247.
2. Singer M., Deutschman C.S., Seymour C.W., Shankar-Hari M., Annane D., Bauer M., et al. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 315(8):801–810.
3. Russell J.A., Walley K.R., Singer J., Gordon A.C., Hébert P.C., Cooper D.J., et al. (2008). Vasopressin versus Norepinephrine Infusion in Patients with Septic Shock. New England Journal of Medicine. 358(9):877–887.
4. Gordon A.C., Mason A.J., Thirunavukkarasu N., Perkins G.D., Cecconi M., et al. (2016). Effect of Early Vasopressin vs Norepinephrine on Kidney Failure in Patients With Septic Shock. JAMA. 316(5):509–518.
5. De Backer D., Biston P., Devriendt J., Madl C., Chochrad D., Aldecoa C., et al. (2010). Comparison of Dopamine and Norepinephrine in the Treatment of Shock. New England Journal of Medicine. 362(9):779–789.
6. Hernández G., Ospina-Tascón G.A., Damiani L.P., Estenssoro E., Dubin A., Hurtado J., et al. (2019). Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels Among Patients With Septic Shock. JAMA. 321(7):654–664.
7. Ospina-Tascón G.A., Teboul J.L., Hernandez G. (2016). Novel biomarkers and hemodynamic monitoring in septic shock. Current Opinion in Critical Care. 22(3):254–261.
8. Cecconi M., Evans L., Levy M., Rhodes A. (2018). Sepsis and septic shock. The Lancet. 392(10141):75–87.
9. Vincent J.L., De Backer D. (2013). Circulatory Shock. New England Journal of Medicine. 369:1726–1734.

10. Annane D., Renault A., Brun-Buisson C., Megarbane B., Quenot J.P., Siami S., et al. (2018). Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. New England Journal of Medicine. 378:809–818.
11. De Backer D., Creteur J., Preiser J.C., Dubois M.J., Vincent J.L. (2002). Microvascular Blood Flow Is Altered in Patients with Sepsis. American Journal of Respiratory and Critical Care Medicine. 166(1):98–104.
12. Myburgh J.A., Mythen M.G. (2013). Resuscitation Fluids. New England Journal of Medicine. 369:1243–1251.
13. Rhodes A., Evans L.E., Alhazzani W., Levy M.M., Antonelli M., Ferrer R., et al. (2017). Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Medicine. 43:304–377.
14. Marik P.E., Khangoora V., Rivera R., Hooper M.H., Catravas J. (2017). Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock. Chest. 151(6):1229–1238.
15. De Backer D., Cecconi M., Lipman J., Machado F., Myatra S.N., Ostermann M., et al. (2019). Challenges in the Management of Septic Shock. Intensive Care Medicine. 45:420–433.
16. Vincent J.L., Moreno R., Takala J., Willatts S., De Mendonça A., Bruining H., et al. (1996). The SOFA Score to Describe Organ Dysfunction/FaiIure. Intensive Care Medicine. 22:707–710.
17. Levy M.M., Evans L.E., Rhodes A. (2018). The Surviving Sepsis Campaign Bundle: 2018 Update. Intensive Care Medicine. 44:925–928.
18. Cecconi M., De Backer D., Antonelli M., Beale R., Bakker J., Hofer C., et al. (2014). Consensus on Circulatory Shock and Hemodynamic Monitoring. Intensive Care Medicine. 40:1795–1815.
19. Evans L., Rhodes A., Alhazzani W., Antonelli M., et al. (2024). Sepsis Management Updates and Future Directions. Critical Care Medicine. 52(1):1–15.

CITATION OF THIS ARTICLE

Muhammad Usama A, Zainab M, M. Rizwan Ishaque, Nida A, Asma S, Obaid A. Comparison of Norepinephrine Alone versus Norepinephrine plus Vasopressin in Refractory Septic Shock: A Prospective Study. Bull. Env. Pharmacol. Life Sci., Vol 15 [7] June 2026. 51-55