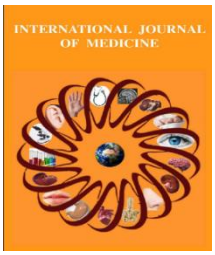

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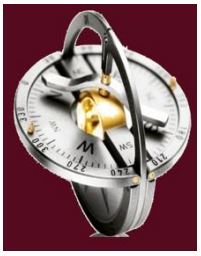

Original Research

Vasopressor Strategies in Septic Shock: Noradrenaline Alone versus Combination Therapy: A Comparative Observational Study.

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Abstract

Introduction: Septic shock is a life-threatening condition associated with high morbidity and mortality despite advances in critical care. Noradrenaline is the recommended first-line vasopressor; however, many patients require additional vasopressor support to achieve adequate hemodynamic stabilization. The comparative effectiveness of noradrenaline alone versus combination vasopressor therapy remains an area of ongoing investigation. This study compared the clinical outcomes of these two vasopressor strategies in patients with septic shock. *Materials and Methods:* A prospective observational comparative study was conducted in the intensive care unit of a tertiary care teaching hospital from July 2024 to July 2025. A total of 150 adult patients with septic shock fulfilling the Sepsis-3 criteria were enrolled and allocated into two groups: noradrenaline alone (n=75) and combination vasopressor therapy (n=75). Baseline demographic and clinical characteristics, vasopressor requirements, organ dysfunction, ICU and hospital stay, vasopressor-free days, ventilator-free days, and 28-day mortality were recorded. Statistical analysis was performed using SPSS version 26.0, with a p-value <0.05 considered statistically significant. *Results:* Baseline characteristics and disease severity were comparable between the two groups. Combination therapy significantly reduced the maximum noradrenaline dose (0.54 ± 0.18 vs. 0.71 ± 0.23 µg/kg/min), shortened the duration of vasopressor therapy (52.7 ± 19.6 vs. 66.8 ± 22.5 hours), and achieved the target mean arterial pressure earlier (5.9 ± 2.8 vs. 8.6 ± 3.5 hours) (all p<0.001). Patients receiving combination therapy also had significantly shorter ICU stay, shorter hospital stay, and more vasopressor-free days (all p<0.05). Although lower rates of acute kidney injury and 28-day mortality were observed in the combination therapy group, these differences were not statistically significant. *Conclusion:* Combination vasopressor therapy provided superior hemodynamic stabilization and improved short-term clinical outcomes compared with noradrenaline alone in patients with septic shock. While mortality benefits were not statistically significant, combination therapy reduced vasopressor requirements and length of hospitalization, supporting its role as an effective adjunctive strategy in the management of septic shock.

Keywords: *Septic shock; Noradrenaline; Vasopressin; Vasopressor therapy; Hemodynamic stabilization.*

Introduction

Septic shock is a life-threatening manifestation of sepsis characterized by profound circulatory, cellular, and metabolic abnormalities that are associated with a substantially increased risk of mortality [1,2]. Despite advances in critical care management, septic shock continues to be one of the leading causes of death among patients admitted to intensive care units (ICUs) worldwide [3]. The condition is marked by persistent hypotension requiring vasopressor therapy to maintain adequate tissue perfusion despite appropriate fluid resuscitation, often accompanied by elevated serum lactate levels indicative of impaired cellular metabolism [4]. Early recognition and prompt hemodynamic stabilization are essential components of management to improve patient outcomes [5].

Noradrenaline is recommended as the first-line vasopressor for the treatment of septic shock because of its potent α-adrenergic vasoconstrictive effects with relatively limited chronotropic activity [6]. However, a considerable proportion of patients remain hypotensive despite escalating doses of noradrenaline, necessitating the addition of a second vasopressor such as vasopressin or adrenaline [7]. Combination vasopressor therapy has been proposed to restore vascular tone through complementary mechanisms of action, reduce catecholamine exposure, improve tissue perfusion, and potentially minimize adverse effects associated with high-dose noradrenaline [8,9]. Current international guidelines advocate individualized vasopressor strategies, yet the optimal timing and clinical benefits of combination therapy remain subjects of ongoing investigation [10].

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Several randomized controlled trials and observational studies have evaluated the efficacy of combination vasopressor therapy in septic shock, reporting variable effects on hemodynamic recovery, vasopressor requirements, organ dysfunction, ICU length of stay, and mortality [11-13]. While some studies have demonstrated earlier achievement of target mean arterial pressure and reduced catecholamine requirements with adjunctive vasopressin, consistent improvements in survival have not been established [14]. Differences in patient characteristics, timing of vasopressor initiation, severity of illness, and treatment protocols have contributed to the heterogeneity of published findings [15]. Consequently, further comparative studies are required to better understand the clinical impact of different vasopressor strategies in routine critical care practice.

The present study aimed to compare the clinical efficacy and outcomes of noradrenaline alone versus combination vasopressor therapy in patients with septic shock by evaluating vasopressor requirements, hemodynamic stabilization, organ dysfunction, length of ICU and hospital stay, and 28-day mortality.

Materials and Methods

This prospective observational comparative study was conducted in the Intensive Care Unit (ICU) of a tertiary care teaching hospital over a period of one year, from July 2024 to July 2025. The study included 150 adult patients diagnosed with septic shock according to the Sepsis-3 criteria, requiring vasopressor support despite adequate fluid resuscitation. Patients aged 18 years and above with persistent hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) of ≥65 mmHg and having a serum lactate level >2 mmol/L were enrolled consecutively. Patients with pregnancy, cardiogenic or hemorrhagic shock, advanced terminal illness, prior long-term vasopressor therapy, or incomplete clinical records were excluded from the study. Institutional Ethics Committee approval was obtained prior to study commencement, and informed consent was obtained from patients or their legally authorized representatives.

Eligible patients were categorized into two treatment groups based on the vasopressor strategy adopted by the treating intensivist. Group A (n=75) received noradrenaline alone, while Group B (n=75) received combination vasopressor therapy comprising noradrenaline with an additional vasopressor (such as vasopressin or adrenaline) according to standard institutional protocols. All patients received guideline-directed management for septic shock, including early antimicrobial therapy, source control, intravenous crystalloid resuscitation, corticosteroids when clinically indicated, organ support, mechanical ventilation, renal replacement therapy, and other supportive measures as required.

Baseline demographic characteristics, comorbidities, source of sepsis, vital parameters, laboratory investigations, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, serum lactate, serum creatinine, and hemodynamic parameters at admission were recorded. Vasopressor-related variables including maximum noradrenaline dose, duration of vasopressor therapy, and time required to achieve the target MAP (≥65 mmHg) were documented. During ICU stay, the occurrence of acute kidney injury, requirement for mechanical ventilation, renal replacement therapy, and cardiac arrhythmias was assessed. Clinical outcomes including ICU length of stay, hospital length of stay, vasopressor-free days, ventilator-free days, and 28-day mortality were evaluated and compared between the two groups.

Data were entered into Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared using the independent samples t-test, while categorical variables were presented as frequencies and percentages and compared using the Chi-square test or Fisher's exact test wherever appropriate. Variables demonstrating clinical relevance or statistical significance in univariate analysis were included in a multivariate logistic regression model to identify independent predictors of 28-day mortality. A two-tailed p-value of <0.05 was considered statistically significant.

Results

A total of 150 patients with septic shock were included in the study, with 75 patients each in the noradrenaline-alone and combination therapy groups. The mean age was comparable between the groups (58.6 ± 13.2 vs. 60.8 ± 12.5 years; p=0.312), and males constituted the majority of the study population (63.3%). The prevalence of diabetes mellitus, hypertension, chronic kidney disease, and chronic liver disease was similar between the two groups, with no statistically significant differences observed (all p>0.05), indicating comparable baseline characteristics (Table 1).

Table 1. Baseline Demographic Characteristics

Variable	Noradrenaline Alone (n=75)	Combination Therapy (n=75)	Total (N=150)	p-value
Age (years), Mean ± SD	58.6 ± 13.2	60.8 ± 12.5	59.7 ± 12.8	0.312
Male	46 (61.3%)	49 (65.3%)	95 (63.3%)	0.611
Female	29 (38.7%)	26 (34.7%)	55 (36.7%)	
BMI (kg/m²), Mean ± SD	24.8 ± 3.7	25.2 ± 4.1	25.0 ± 3.9	0.548
Diabetes Mellitus	29 (38.7%)	31 (41.3%)	60 (40.0%)	0.741
Hypertension	34 (45.3%)	37 (49.3%)	71 (47.3%)	0.623
Chronic Kidney Disease	9 (12.0%)	11 (14.7%)	20 (13.3%)	0.629
Chronic Liver Disease	6 (8.0%)	8 (10.7%)	14 (9.3%)	0.570

Pneumonia was the most common source of sepsis, accounting for 38.7% of all cases, followed by urinary tract infections (22.0%) and intra-abdominal infections (18.0%). Skin and soft tissue infections and bloodstream infections were less frequent. The distribution of infection sources was comparable between the noradrenaline-alone and combination therapy groups without any statistically significant difference (p=0.912) (Table 2).

Table 2. Source of Sepsis

Source	Noradrenaline Alone	Combination Therapy	Total	p-value
Pneumonia	28 (37.3%)	30 (40.0%)	58 (38.7%)	0.912
Urinary tract infection	17 (22.7%)	16 (21.3%)	33 (22.0%)	
Intra-abdominal infection	14 (18.7%)	13 (17.3%)	27 (18.0%)	
Skin/Soft tissue infection	9 (12.0%)	8 (10.7%)	17 (11.3%)	
Bloodstream infection	7 (9.3%)	8 (10.7%)	15 (10.0%)	

At admission, the two treatment groups demonstrated similar clinical severity. Mean arterial pressure, heart rate, serum lactate, SOFA score, APACHE II score, and serum creatinine levels were comparable between the groups, with no statistically significant differences (all p>0.05), suggesting equivalent baseline hemodynamic status and disease severity prior to initiation of vasopressor therapy (Table 3).

Table 3. Baseline Clinical Parameters

Variable	Noradrenaline Alone	Combination Therapy	p-value
MAP (mmHg)	56.8 ± 6.1	55.9 ± 5.8	0.372
Heart Rate (beats/min)	118.6 ± 18.5	120.3 ± 17.2	0.561

Lactate (mmol/L)	4.6 ± 1.7	4.8 ± 1.9	0.478
SOFA Score	9.8 ± 2.4	10.2 ± 2.5	0.324
APACHE II Score	21.7 ± 5.8	22.4 ± 5.5	0.459
Serum Creatinine (mg/dL)	1.82 ± 0.74	1.95 ± 0.82	0.317

Patients receiving combination vasopressor therapy required a significantly lower maximum noradrenaline dose (0.54 ± 0.18 vs. 0.71 ± 0.23 µg/kg/min; p<0.001), achieved the target mean arterial pressure (≥65 mmHg) earlier (5.9 ± 2.8 vs. 8.6 ± 3.5 hours; p<0.001), and had a shorter duration of vasopressor support (52.7 ± 19.6 vs. 66.8 ± 22.5 hours; p<0.001) compared with patients receiving noradrenaline alone (Table 4).

Table 4. Vasopressor Requirements

Variable	Noradrenaline Alone	Combination Therapy	p-value
Maximum Noradrenaline dose (µg/kg/min)	0.71 ± 0.23	0.54 ± 0.18	<0.001
Duration of Vasopressor Therapy (hours)	66.8 ± 22.5	52.7 ± 19.6	<0.001
Time to MAP ≥65 mmHg (hours)	8.6 ± 3.5	5.9 ± 2.8	<0.001

The incidence of acute kidney injury, requirement for renal replacement therapy, need for mechanical ventilation, and occurrence of arrhythmias were lower in the combination therapy group than in the noradrenaline-alone group; however, these differences did not reach statistical significance (all p>0.05), indicating a favorable but non-significant trend toward reduced organ dysfunction with combination therapy (Table 5).

Table 5. Organ Dysfunction During ICU Stay

Variable	Noradrenaline Alone	Combination Therapy	p-value
Acute Kidney Injury	31 (41.3%)	22 (29.3%)	0.122
Mechanical Ventilation	39 (52.0%)	33 (44.0%)	0.325
Renal Replacement Therapy	17 (22.7%)	11 (14.7%)	0.206
Arrhythmias	14 (18.7%)	10 (13.3%)	0.369

Combination therapy was associated with significantly shorter ICU stay (7.2 ± 2.8 vs. 8.9 ± 3.4 days; p=0.001), shorter hospital stay (11.8 ± 4.2 vs. 13.6 ± 4.9 days; p=0.018), and a greater number of vasopressor-free days (20.3 ± 4.8 vs. 17.4 ± 5.1 days; p=0.001). Although ventilator-free days were marginally higher and 28-day mortality was lower in the combination therapy group, these differences were not statistically significant (p>0.05) (Table 6).

Table 6. Clinical Outcomes

Variable	Noradrenaline Alone	Combination Therapy	p-value
ICU Stay (days)	8.9 ± 3.4	7.2 ± 2.8	0.001
Hospital Stay (days)	13.6 ± 4.9	11.8 ± 4.2	0.018
Vasopressor-free Days	17.4 ± 5.1	20.3 ± 4.8	0.001
Ventilator-free Days	18.6 ± 6.2	20.1 ± 5.8	0.126
28-day Mortality	24 (32.0%)	16 (21.3%)	0.141

Multivariate logistic regression identified increasing age (adjusted OR 1.03; p=0.014), higher serum lactate (adjusted OR 1.29; p=0.005), higher SOFA score (adjusted OR 1.24; p=0.002), and higher APACHE II score (adjusted OR 1.11; p=0.011) as independent predictors of 28-day mortality. Although combination vasopressor therapy showed a lower adjusted odds of mortality (adjusted OR 0.63), the association was not statistically significant (p=0.214) (Table 7).

Table 7. Multivariate Logistic Regression for 28-day Mortality

Variable	Adjusted OR	95% CI	p-value
Combination Therapy	0.63	0.30-1.31	0.214
Age	1.03	1.01-1.06	0.014
Lactate	1.29	1.08-1.55	0.005
SOFA Score	1.24	1.08-1.42	0.002
APACHE II Score	1.11	1.02-1.20	0.011

Discussion

The present study compared the effectiveness of noradrenaline alone with combination vasopressor therapy in patients with septic shock. Baseline demographic characteristics, comorbidities, source of infection, and illness severity scores were comparable between the two groups, ensuring an unbiased comparison of treatment outcomes. Our findings demonstrated that combination therapy was associated with significantly lower maximum noradrenaline requirements, earlier achievement of target mean arterial pressure (MAP ≥65 mmHg), and shorter duration of vasopressor support. These observations are consistent with the physiological rationale that vasopressin or other adjunctive vasopressors restore vascular tone through non-catecholamine pathways, thereby reducing catecholamine exposure. Similar findings were reported in the VASST trial by Russell et al., which demonstrated reduced norepinephrine requirements with adjunctive vasopressin, although no overall mortality benefit was observed [16]. Likewise, the recent REVISE trial also reported improved vasopressor efficiency without a significant reduction in mortality with vasopressin-based strategies [17].

An important finding of the present study was the significantly shorter ICU stay, hospital stay, and greater number of vasopressor-free days in patients receiving combination therapy. Earlier restoration of adequate tissue perfusion and reduced dependence on high-dose catecholamines may have contributed to faster clinical recovery. Although the incidence of acute kidney injury, need for renal replacement therapy, mechanical ventilation, and arrhythmias was lower in the combination therapy group, these differences did not reach statistical significance. Similar observations have been reported in the VANISH trial by Gordon et al., where early vasopressin administration reduced catecholamine exposure and suggested improved renal outcomes without significantly affecting overall mortality [18].

In the present study, 28-day mortality was numerically lower in the combination therapy group (21.3% vs. 32.0%), although the difference was not statistically significant. This finding is comparable to the VASST and REVISE trials, both of which demonstrated no significant overall survival advantage of combination vasopressor therapy despite improvements in hemodynamic parameters [16,17]. Septic shock mortality is influenced by multiple factors beyond vasopressor choice, including timing of antimicrobial therapy, adequacy of source control, severity of organ dysfunction, and underlying comorbidities. Therefore, while combination therapy may facilitate hemodynamic stabilization and reduce vasopressor exposure, its independent effect on mortality remains uncertain and likely depends on appropriate patient selection and early initiation of comprehensive sepsis management.

Multivariate logistic regression in the present study identified increasing age, elevated serum lactate, higher SOFA score, and higher APACHE

II score as independent predictors of 28-day mortality. These findings are consistent with previous literature identifying these variables as reliable indicators of disease severity and poor prognosis in septic shock. The absence of an independent mortality benefit with combination vasopressor therapy in our analysis further supports current evidence suggesting that adjunctive vasopressors primarily improve hemodynamic stabilization rather than survival. Overall, the present study indicates that combination vasopressor therapy is an effective strategy for reducing catecholamine requirements and accelerating hemodynamic recovery while producing favorable trends in clinical outcomes. Larger multicenter randomized studies are warranted to determine whether these hemodynamic advantages translate into meaningful long-term survival benefits.

Conclusion

The present study demonstrates that combination vasopressor therapy in patients with septic shock provides superior hemodynamic stabilization compared with noradrenaline alone by reducing maximum noradrenaline requirements, shortening the duration of vasopressor support, achieving target mean arterial pressure more rapidly, and decreasing ICU and hospital length of stay. Although combination therapy showed favorable trends toward lower organ dysfunction and 28-day mortality, these differences were not statistically significant. Overall, the findings suggest that combination vasopressor therapy is a safe and effective strategy for optimizing hemodynamic management in septic shock, while larger multicenter randomized studies are required to establish its impact on long-term survival and clinical outcomes.

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