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Comparison of Early Norepinephrine Administration Versus Standard Treatment in Patients With Septic Shock

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Abstract

Septic shock is a life-threatening condition characterized by profound circulatory dysfunction and persistent hypotension, requiring rapid hemodynamic stabilization. The objective of this study was to compare the effectiveness of early norepinephrine administration with standard treatment in achieving shock control among patients with septic shock. A randomized controlled trial was conducted in the Department of Medicine, Provincial Headquarter Hospital, Gilgit, from May 2026 to August 2026. A total of 106 patients aged 18–65 years with septic shock were enrolled through non-probability consecutive sampling and randomly allocated equally to an early norepinephrine group and a standard-treatment group, with 53 patients in each group. Both groups received standard septic shock management, including crystalloid resuscitation, antibiotics, source control, and organ support. The mean age was 49.1 ± 11.8 years in the early norepinephrine group and 50.4 ± 12.2 years in the standard-treatment

group ($p = 0.578$). Baseline mean arterial pressure was also comparable between the groups (56.7 ± 5.8 vs. 57.4 ± 6.1 mmHg; $p = 0.546$). Shock control was achieved in 40 (75.5%) patients receiving early norepinephrine compared with 26 (49.1%) patients receiving standard treatment ($\chi^2 = 7.88$, $p = 0.005$). Mean arterial pressure at 1 hour was significantly higher in the early norepinephrine group (68.9 ± 7.0 vs. 63.2 ± 7.6 mmHg; $p < 0.001$), with significant differences persisting at 6 hours (73.8 ± 6.6 vs. 68.5 ± 7.4 mmHg; $p < 0.001$) and 24 hours (76.1 ± 7.1 vs. 71.9 ± 7.8 mmHg; $p = 0.005$). These findings indicate that early norepinephrine administration was more effective than standard treatment in achieving shock control and produced a more rapid improvement in mean arterial pressure among patients with septic shock.

Keywords: septic shock, norepinephrine, vasopressor, shock control, mean arterial pressure, hemodynamic stabilization

1. INTRODUCTION

Septic shock is characterized by profound systemic vasodilation, altered vascular tone, and increased vascular permeability associated with a dysregulated response to severe infection [1, 2]. In patients with sepsis, persistent hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) of ≥ 65 mmHg together with a blood lactate concentration greater than 18 mg/dL (2 mmol/L), despite adequate volume resuscitation, is consistent with septic shock [1]. In addition to specific treatment of the infection, including timely antimicrobial therapy and source control, management depends on appropriate organ support and correction of hemodynamic derangements [2, 3]. Initial intravenous fluid resuscitation is used to optimize intravascular volume, and vasopressors are administered when adequate fluid resuscitation does not achieve the required blood-pressure target [1, 2].

A growing body of research has examined the potential benefits of initiating norepinephrine (NE) early during resuscitation. Experimental work in early-stage endotoxemic shock indicates that appropriately dosed norepinephrine can improve mean arterial pressure, reduce fluid requirements, and support microcirculatory perfusion, although the hemodynamic response varies according to dose [4, 5]. NE is a potent arterial vasoconstrictor that increases vascular tone and thereby raises perfusion pressure [2]. In addition, its venoconstrictive effects can increase stressed blood volume, venous return, cardiac preload, and, in suitable patients, cardiac output [6, 7]. These combined arterial and venous effects provide a physiological rationale for considering norepinephrine early when hypotension persists during septic-shock resuscitation.

Permpikul et al. included 310 adult patients with sepsis-associated hypotension in two equally sized groups: an early norepinephrine (NE) group and a standard-treatment group. The shock-control rate at 6 hours was significantly higher in the early-NE group than in the standard-treatment group (76.1% vs. 48.4%). There was no statistically significant difference in 28-day mortality, which was 15.5% in the early-NE group and 21.9% in the standard-treatment group. Early NE was also associated with lower incidences of cardiogenic pulmonary edema (14.4% vs. 27.7%) and new-onset arrhythmia (11% vs. 20%) [8]. Bai et al. compared early and delayed NE administration in 213 adult patients with septic shock. Mortality was 27.5%, 30.4%, and 65.2% when norepinephrine was initiated within <1 hour, from 1–2 hours, or ≥ 6 hours after the onset of septic shock, respectively [9]. Other studies have likewise examined whether very early norepinephrine initiation is associated with improved hemodynamic and clinical outcomes [10–13]. The present study was therefore planned to assess whether earlier administration of low-dose NE in patients with sepsis-associated hypotension improves the achievement of shock control. The findings may help clarify the timing of NE initiation and may have direct relevance to the local management of septic shock. If early norepinephrine provides a clinically meaningful benefit, earlier intervention could improve hemodynamic stabilization and potentially reduce complications associated with prolonged hypotension.

The objective of this study was to investigate whether early administration of norepinephrine is more effective than standard therapy among patients with septic shock.

2. METHODOLOGY

This study was a randomized controlled trial (RCT) conducted in the Department of Medicine, Provincial Headquarter Hospital, Gilgit, from May 2026 to August 2026. The sample size was determined using OpenEpi for a two-proportion comparison in a randomized controlled trial. Using a shock-control rate of 76.1% for early norepinephrine and 48.4% for the standard-treatment group, with 80% statistical power and a 5% level of significance, the required sample size was calculated as 106 patients. The patients were then randomly allocated to two groups, with 53 patients in each group [8]. A non-probability consecutive sampling technique was used for recruitment. Patients who met the eligibility criteria were recruited consecutively until the target sample size had been achieved. Male and female patients aged 18–65 years who met the septic shock criterion defined above were eligible for enrollment. The exclusion criteria included advanced malignancy, acute coronary syndrome, acute cerebrovascular events, acute pulmonary edema, acute asthma, active cardiac arrhythmias, active gastrointestinal bleeding, pregnancy, active convulsions, drug overdose, burns, accidental trauma, and any condition requiring urgent surgical intervention. These conditions were identified from the available clinical history, physical examination, and medical records.

After enrollment, participants were randomly allocated in a 1:1 ratio to the early norepinephrine group (Group A) or the standard-treatment group (Group B) using blocked randomization. The randomization sequence was generated before participant recruitment. Study infusions were prepared by the pharmacy department after treatment allocation. Participants remained unaware of the treatment assigned to them, and the outcome assessor was also blinded to treatment allocation. These procedures were used to reduce the potential for performance and assessment bias during the trial.

Before the study was initiated, approval was obtained from the institutional ethics review committee and the College of Physicians and Surgeons Pakistan. After written informed consent had been obtained, a total of 106 eligible patients presenting to the Department of Medicine were enrolled. Demographic and clinical data were collected on a structured baseline proforma. The recorded variables included age, sex, residence (rural or urban), educational status, socioeconomic status, obesity, diabetes mellitus, hypertension, and the primary site of infection. Infections were classified as respiratory,

intra-abdominal, genitourinary, bloodstream, or skin and soft-tissue infection. Both groups received the same standard management of septic shock, including organ support, source control, antimicrobial therapy, and intravenous crystalloid resuscitation according to institutional practice. Patients in Group A received early norepinephrine. Four milligrams of norepinephrine were mixed in 250 mL of 5% dextrose water, producing a final concentration of 16 $\mu\text{g/mL}$. Patients were given 250 mL of 5% dextrose water at the same infusion rate and for the same duration, in addition to the norepinephrine dose calculated according to individual body weight. The study infusion was administered for 24 hours to both groups according to the study protocol. Blood pressure was measured at enrollment and every 15 minutes thereafter using an automated non-invasive blood-pressure (NIBP) monitor or an arterial line when available. Other relevant hemodynamic observations, including mean arterial pressure, were also recorded. Shock control was determined according to the predefined operational definition. The outcome assessor remained blinded to group allocation, and all observations and outcomes were documented on the predesigned structured proforma. Shock control was the primary outcome. The proportion of patients achieving shock control was compared between the early norepinephrine and standard-treatment groups according to the predefined operational criterion.

The data were entered into and analyzed using SPSS version 23.0. The Shapiro–Wilk test was used to assess the normality of numerical variables. Normally distributed quantitative variables, including age, mean arterial pressure at enrollment, and systolic and diastolic blood pressure, were reported as mean $\pm$ standard deviation (SD). Non-normally distributed numerical variables were presented as median and interquartile range (IQR). Categorical variables, including sex, area of residence, education, socioeconomic status, obesity, diabetes mellitus, hypertension, primary infection site, and shock control, were presented as frequencies and percentages. The chi-square test was used to compare the proportion of patients achieving shock control between the two study groups. Fisher's exact test was applied when expected cell counts were too small for an appropriate chi-square test. A p-value of ≤ 0.05 was considered statistically significant. Potential effect modification was examined by stratification according to age, sex, geographic area of residence, level of education, socioeconomic status, obesity, diabetes mellitus, hypertension, and primary infection site. After stratification, the chi-square test or Fisher's exact test, as applicable, was used to compare shock control between the two treatment groups within each stratum.

3. RESULTS

Data were collected from 106 patients. The mean age was 49.1 ± 11.8 years in the early norepinephrine group and 50.4 ± 12.2 years in the standard-treatment group ($t = -0.56$, $p = 0.578$). Males constituted 31 (58.5%) and 29 (54.7%) patients, respectively ($\chi^2 = 0.16$, $p = 0.694$), whereas females accounted for 22 (41.5%) and 24 (45.3%) patients. Rural residence was reported in 34 (64.2%) versus 36 (67.9%) patients ($\chi^2 = 0.17$, $p = 0.681$). Obesity was present in 12 (22.6%) versus 10 (18.9%) patients ($\chi^2 = 0.23$, $p = 0.634$), diabetes mellitus in 19 (35.8%) versus 21 (39.6%) patients ($\chi^2 = 0.16$, $p = 0.690$), and hypertension in 23 (43.4%) versus 25 (47.2%) patients ($\chi^2 = 0.15$, $p = 0.695$). The baseline demographic, clinical, and hemodynamic characteristics of both groups are summarized in Table 1.

Table 1. Baseline demographic, clinical, and hemodynamic characteristics of study participants

Variable	Early norepinephrine (n = 53)	Standard treatment (n = 53)	Test statistic	p-value
Age, years	49.1 ± 11.8	50.4 ± 12.2	$t = -0.56$	0.578
Male sex	31 (58.5%)	29 (54.7%)	$\chi^2 = 0.16$	0.694
Female sex	22 (41.5%)	24 (45.3%)		
Rural residence	34 (64.2%)	36 (67.9%)	$\chi^2 = 0.17$	0.681
Urban residence	19 (35.8%)	17 (32.1%)		
Obesity	12 (22.6%)	10 (18.9%)	$\chi^2 = 0.23$	0.634
Diabetes mellitus	19 (35.8%)	21 (39.6%)	$\chi^2 = 0.16$	0.690
Hypertension	23 (43.4%)	25 (47.2%)	$\chi^2 = 0.15$	0.695
Systolic blood pressure, mmHg	78.6 ± 7.9	79.3 ± 8.2	$t = -0.45$	0.655
Diastolic blood pressure, mmHg	45.8 ± 6.7	46.4 ± 7.1	$t = -0.45$	0.655
Mean arterial pressure, mmHg	56.7 ± 5.8	57.4 ± 6.1	$t = -0.61$	0.546

Respiratory infection was the most common primary infection site in both groups, occurring in 21 (39.6%) patients in the early norepinephrine group and 20 (37.7%) patients in the standard-treatment group. Intra-abdominal infection was present in 10 (18.9%) versus 11 (20.8%) patients, genitourinary infection in 9 (17.0%) versus 10 (18.9%) patients, bloodstream infection in 8 (15.1%) versus 7 (13.2%) patients, and skin and soft-tissue infection in 5 (9.4%) patients in each group. The complete distribution of primary infection sites between the two treatment groups is presented in Table 2.

Table 2. Distribution of primary infection site between treatment groups

Primary infection site	Early norepinephrine (n = 53)	Standard treatment (n = 53)	Test statistic	p-value
Respiratory	21 (39.6%)	20 (37.7%)		
Intra-abdominal	10 (18.9%)	11 (20.8%)		
Genitourinary	9 (17.0%)	10 (18.9%)		
Bloodstream	8 (15.1%)	7 (13.2%)		
Skin and soft tissue	5 (9.4%)	5 (9.4%)	$\chi^2 = 0.61$	0.961

Shock control was achieved in 40 (75.5%) patients receiving early norepinephrine compared with 26 (49.1%) patients receiving standard treatment. In contrast, shock was not controlled in 13 (24.5%) patients in the early norepinephrine group and 27 (50.9%) patients in the standard-treatment group. This between-group difference was statistically significant ($\chi^2 = 7.88$, $p = 0.005$), as shown in Table 3.

Table 3. Comparison of shock control between early norepinephrine and standard treatment

Shock control	Early norepinephrine (n = 53)	Standard treatment (n = 53)	Test statistic	p-value
Achieved	40 (75.5%)	26 (49.1%)		
Not achieved	13 (24.5%)	27 (50.9%)	$\chi^2 = 7.88$	0.005

Mean arterial pressure at enrollment was comparable between the early norepinephrine and standard-treatment groups at 56.7 ± 5.8 and 57.4 ± 6.1 mmHg, respectively ($t = -0.61$, $p = 0.546$). At 1 hour, MAP increased to 68.9 ± 7.0 mmHg in the early norepinephrine group compared with 63.2 ± 7.6 mmHg in the standard-treatment group ($t = 4.02$, $p < 0.001$). At 6 hours, MAP was 73.8 ± 6.6 versus 68.5 ± 7.4 mmHg ($t = 3.89$, $p < 0.001$), whereas at 24 hours it was 76.1 ± 7.1 versus 71.9 ± 7.8 mmHg ($t = 2.90$, $p = 0.005$). The full comparison of the hemodynamic response, including the increase in MAP at 1 hour, is provided in Table 4.

Table 4. Comparison of hemodynamic response between treatment groups

Hemodynamic parameter	Early norepinephrine (n = 53)	Standard treatment (n = 53)	Test statistic	p-value
MAP at enrollment, mmHg	56.7 ± 5.8	57.4 ± 6.1	$t = -0.61$	0.546
MAP at 1 hour, mmHg	68.9 ± 7.0	63.2 ± 7.6	$t = 4.02$	<0.001
MAP at 6 hours, mmHg	73.8 ± 6.6	68.5 ± 7.4	$t = 3.89$	<0.001
MAP at 24 hours, mmHg	76.1 ± 7.1	71.9 ± 7.8	$t = 2.90$	0.005
Increase in MAP at 1 hour, mmHg	12.2 ± 6.4	5.8 ± 5.9	$t = 5.35$	<0.001

Among patients aged ≤ 50 years, shock control was achieved in 21/27 (77.8%) versus 14/28 (50.0%) patients ($\chi^2 = 4.59$, $p = 0.032$), whereas among those aged > 50 years the rates were 19/26 (73.1%) versus 12/25 (48.0%) ($p = 0.066$). Among males, shock control occurred in 24/31 (77.4%) versus 15/29 (51.7%) patients ($p = 0.037$), whereas among females it occurred in 16/22 (72.7%) versus 11/24 (45.8%) patients ($p = 0.065$). In patients without diabetes, shock control was significantly higher with early norepinephrine, at 27/34 (79.4%) versus 17/32 (53.1%) patients ($p = 0.023$), and among those without hypertension it was 24/30 (80.0%) versus 14/28 (50.0%) patients ($p = 0.016$). The complete stratified comparison, including respiratory and non-respiratory infection subgroups, is presented in Table 5.

Table 5. Stratified comparison of shock control between treatment groups

Subgroup	Early norepinephrine shock control, n/N (%)	Standard treatment shock control, n/N (%)	Test statistic	p-value
Age ≤ 50 years	21/27 (77.8%)	14/28 (50.0%)	$\chi^2 = 4.59$	0.032
Age > 50 years	19/26 (73.1%)	12/25 (48.0%)	$\chi^2 = 3.38$	0.066
Male	24/31 (77.4%)	15/29 (51.7%)	$\chi^2 = 4.34$	0.037
Female	16/22 (72.7%)	11/24 (45.8%)	$\chi^2 = 3.41$	0.065
Diabetes mellitus	13/19 (68.4%)	9/21 (42.9%)	$\chi^2 = 2.65$	0.104
No diabetes mellitus	27/34 (79.4%)	17/32 (53.1%)	$\chi^2 = 5.17$	0.023
Hypertension	16/23 (69.6%)	12/25 (48.0%)	$\chi^2 = 2.37$	0.124
No hypertension	24/30 (80.0%)	14/28 (50.0%)	$\chi^2 = 5.83$	0.016
Respiratory infection	15/21 (71.4%)	10/20 (50.0%)	$\chi^2 = 1.97$	0.160
Non-respiratory infection	25/32 (78.1%)	16/33 (48.5%)	$\chi^2 = 6.08$	0.014

The higher proportion of patients achieving shock control with early norepinephrine is illustrated in Figure 1. The pattern of mean arterial pressure over the 24-hour observation period for both treatment groups is shown in Figure 2.

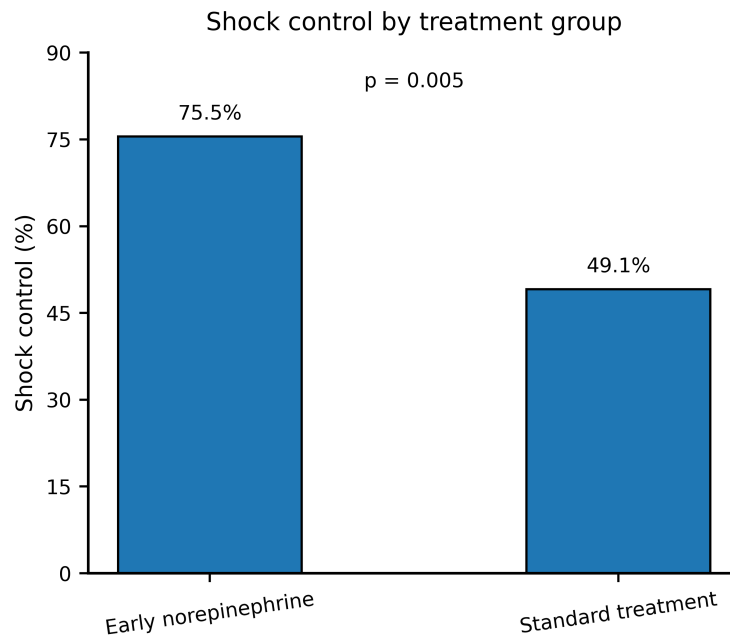


Figure 1. Shock control by treatment group

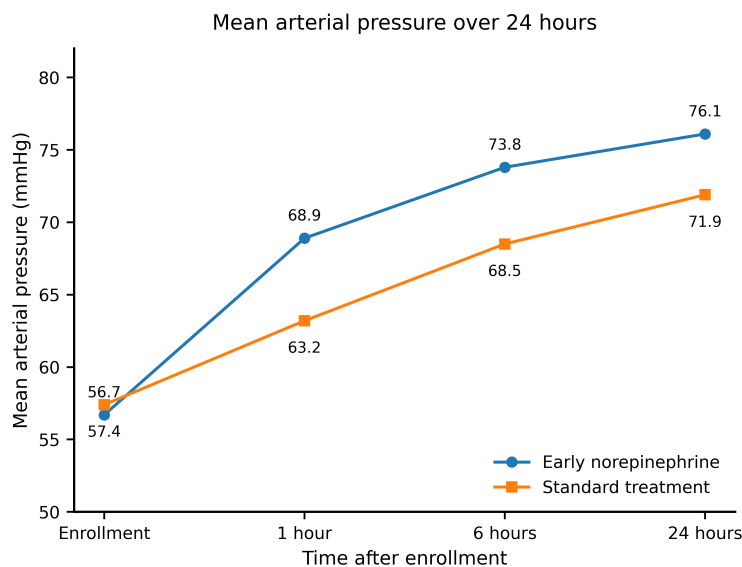


Figure 2. Mean arterial pressure over 24 hours in the two treatment groups

4. DISCUSSION

The current randomized controlled trial (RCT) compared early norepinephrine treatment with standard therapy in patients with septic shock. The principal finding was that early norepinephrine was associated with significantly better shock control. Shock control was achieved more frequently in the early norepinephrine group (75.5%) than in the standard-treatment group (49.1%), and this difference was statistically significant ($p = 0.005$). Furthermore, patients in the early norepinephrine group demonstrated a more rapid improvement in mean arterial pressure during the first 24 hours. These results support the hypothesis that earlier restoration of vascular tone may be beneficial during the initial management of septic shock. Baseline characteristics were similar between the two treatment groups, including age, sex, residence, obesity, pre-existing diabetes mellitus, hypertension, and baseline blood-pressure measurements. Mean arterial pressure at enrollment was also comparable between the groups, indicating that the subsequent differences in hemodynamic response were unlikely to have resulted from major baseline imbalances. This consideration is important because the initial severity and duration of hypotension may influence vasopressor response and clinical prognosis [8–10, 14].

The most clinically important result of this study was the significantly greater proportion of patients who achieved shock control with early norepinephrine. Previous studies have similarly shown that earlier norepinephrine administration

during resuscitation can increase the likelihood of reaching the target blood pressure and achieving early shock control. In the CENSER randomized trial, early low-dose norepinephrine was associated with a substantially higher rate of shock control at 6 hours than standard treatment [8]. Propensity-score analyses have also reported potential benefits associated with very early or earlier initiation of norepinephrine in septic shock [11, 12]. These findings are consistent with the present results and with the physiological rationale for initiating vasopressor therapy before hypotension becomes prolonged. The increase in systemic vascular resistance after norepinephrine administration may contribute to this beneficial hemodynamic effect. Septic shock involves profound vasodilation, loss of vascular tone, and redistribution of vascular blood volume [2]. Norepinephrine acts predominantly through alpha-adrenergic receptors to increase vascular tone and mean arterial pressure, while its venous effects can also modify venous return [6, 7]. Re-establishing perfusion pressure as early as possible may help preserve organ perfusion and minimize the duration of tissue hypoperfusion. Conversely, delayed vasopressor initiation can expose patients to a longer period of hypotension, and observational evidence has associated delayed vasopressor administration with less favorable outcomes [9, 13].

In the present study, mean arterial pressure at 1, 6, and 24 hours was also significantly higher in the early norepinephrine group. At 1 hour, the mean arterial pressures were 68.9 ± 7.0 mmHg in the early norepinephrine group and 63.2 ± 7.6 mmHg in the standard-treatment group. The between-group difference remained evident at the subsequent 6-hour and 24-hour measurements. These findings are consistent with previous evidence indicating that earlier norepinephrine initiation can facilitate more rapid attainment of the target mean arterial pressure [8, 10]. Norepinephrine may also exert an inotropic effect during the early phase of septic shock, which can contribute to hemodynamic improvement in appropriately selected patients [15]. The early improvement in arterial pressure may be particularly relevant because both the severity and duration of hypotension have been associated with adverse outcomes in septic patients [14]. Evidence comparing vasoactive agents has also supported norepinephrine as an appropriate first-line catecholamine in septic shock; for example, comparative data with dopamine demonstrated clinically important differences in efficacy and safety [16]. Trials comparing norepinephrine with other vasopressors, including vasopressin, have further defined the broader vasopressor strategy used in septic shock, although such studies did not specifically test the timing question addressed here [17].

Another possible benefit of early norepinephrine is its potential to reduce excessive fluid administration. Although adequate fluid resuscitation remains essential in septic-shock therapy, large crystalloid volumes can contribute to pulmonary edema, tissue edema, impaired oxygen diffusion, increased venous pressures, and compromised organ function. Earlier vasopressor therapy may therefore permit a more judicious resuscitation strategy by restoring vascular tone while avoiding unnecessary fluid loading. Studies examining early norepinephrine have reported lower resuscitation fluid requirements and potentially more favorable clinical outcomes when vasopressor support is initiated earlier [9–11]. These findings may also be relevant in resource-limited environments. Rapid stabilization of hypotension with a widely available vasopressor such as norepinephrine may provide a practical therapeutic advantage in hospitals that do not have access to sophisticated hemodynamic monitoring. Early initiation may be particularly useful in patients presenting late or with severe vasodilatory shock. When central venous access is not immediately available, evidence from early septic shock cohorts indicates that vasopressor initiation through appropriately monitored peripheral venous access can shorten the time to treatment without a demonstrated adjusted increase in mortality, although careful local protocols remain necessary [18]. Nevertheless, norepinephrine administration must accompany, rather than replace, individualized fluid resuscitation, timely antimicrobial therapy, source control, assessment of tissue perfusion, appropriate organ support, and careful blood-pressure monitoring [1, 3]. Septic shock is a multifactorial clinical disorder in which outcome depends on adequate oxygenation, fluid responsiveness, overall volume status, timely antibiotics, effective control of the infection source, organ support, and underlying comorbidities. Therefore, the improvement in early hemodynamic stabilization observed in this study should be interpreted as one component of a comprehensive resuscitation strategy rather than as an isolated intervention.

5. LIMITATIONS

There were several limitations to this study. First, the study was conducted at a single tertiary-care center and included a relatively small sample of 106 patients, which may restrict the generalizability of the findings to other hospitals, healthcare settings, and patient populations. Second, the study focused primarily on shock control and short-term hemodynamic response, whereas important clinical endpoints such as 28-day mortality, ICU length of stay, duration of vasopressor use, number of organ failures, need for mechanical ventilation, and number of vasopressor-free days were not assessed. Third, despite randomization, some uncontrolled variables may have influenced treatment outcomes, including illness severity, pretreatment lactate concentration, volume status, timing of antibiotic administration, and adequacy of infection-source control. Fourth, detailed information regarding the total amount of intravenous fluid administered, cumulative norepinephrine exposure, and the amount of rescue vasopressor therapy required was not included; therefore, the overall resuscitation strategy could not be assessed comprehensively. Larger multicenter randomized trials incorporating validated severity scores, detailed fluid balance, organ-dysfunction measures, adverse events, and mortality outcomes would be valuable for confirming and extending these findings.

6. CONCLUSION

The findings of this study indicate that early administration of norepinephrine is more effective than standard therapy for achieving shock control in patients with septic shock. Patients who received early norepinephrine had a significantly higher rate of shock control and a more rapid increase in mean arterial pressure during the first 24 hours after treatment. These results suggest that restoration of vascular tone at an earlier stage may improve initial hemodynamic stabilization and may reduce the duration of clinically important hypotension. Early norepinephrine could therefore represent a valuable component of septic-shock resuscitation when used together with targeted fluid resuscitation, timely antimicrobial therapy, source control, careful perfusion assessment, and appropriate organ support. The present findings should, however, be interpreted in the context of the study limitations and require confirmation in larger multicenter trials with additional patient-centered outcomes.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the conception, development, preparation, and revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY

No new dataset was generated or analyzed.

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