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ORIGINAL RESEARCH INTENSIVE CARE

Impact of early versus late administration of norepinephrine on the hemodynamic outcome and mortality in septic shock

Sarah Hamdy Elghareeb [1], Hassan Yasser Mohamed [2], Azza Atef Abd Elaleem [3], Mohamed Salah Mahmoud [4]

Authors affiliations:

1. Sarah Hamdy Elghareeb. Lecturer, Department of Anesthesiology, ICU & Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt Email: Sarahhamdy@med.asu.edu.eg, {ORCID:0000-0001-8050-509X}
2. Hassan Yasser Mohamed, Resident, Department of Anesthesiology, ICU & Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt Email: hassanyasser27697@gmail.com
3. Azza Atef Abd Elaleem, Professor of Anesthesiology, ICU & Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt Email: azza_attef@med.asu.edu.eg
4. Mohamed Salah Mahmoud, Lecturer, Department of Anesthesiology, ICU & Pain Management, Faculty of Medicine, Ain Shams University, Cairo, Egypt Email: doctor_salah2005@hotmail.com

Correspondence: Sarah Hamdy Elghareeb, **Email:** Sarahhamdy@med.asu.edu.eg

ABSTRACT

Background & objective: It has been hypothesized that norepinephrine (NE) administration during the early phases of septic shock will improve survival and hemodynamic outcomes by rapidly restoring perfusion. This study compares the effects of early (< 2 hours) versus late (≥ 2 hours) NE administration in patients of septic shock on mortality and secondary outcomes.

Methodology: A prospective, double-blind, randomized controlled trial involving 200 adult patients with septic shock was conducted in the ICU of Faculty of Medicine, Ain Shams University, Cairo. The participants were assigned to either Group A, to receive early NE administration; or Group B, to receive NE ≥ 2 hours later in their treatment protocol. Key outcomes measured included mortality rate, hemodynamic parameters, serum lactate clearance, NE dosage, and length of hospital stay (LOS). Statistical analyses were conducted with chi-square and Mann-Whitney tests to determine significance of the results.

Results: Group A exhibited a significantly reduced 28-30 days mortality rate compared to Group B, with rates of 28% versus 46% (P = 0.008). The time required to reach the target mean arterial pressure (MAP) of ≥ 65 mmHg was significantly shorter for Group A; 1.0 ± 0.5 days vs. 1.5 ± 0.4 days in Group B (P < 0.01). Lactate clearance in Group A was markedly superior; 40.7% compared to 14.8% in Group B (P < 0.01). Patients in Group A required lower doses of NE, averaging 29.4 ± 9.7 mg versus 32.8 ± 10.0 mg in Group B (P < 0.01), and for a shorter duration of 2.6 ± 0.6 days compared to 2.9 ± 1.0 days (P = 0.038). However, LOS in Group A was slightly more than Group B, averaging 12.5 ± 8.5 days vs. 11.0 ± 6.0 days (P = 0.003). Serum lactate, creatinine, and C-reactive protein (CRP) levels were also higher in Group B, indicating a higher level of organ failure and systemic inflammation.

Conclusion: Early norepinephrine administration in septic shock patients results in improved hemodynamic and metabolic parameters as well as a notable decrease in death rates compared to delayed use of norepinephrine, highlighting the importance of prompt vasopressor use in sepsis treatment protocols.

Abbreviations: BMI: Body mass Index, CRP: C-reactive Protein, IVF: Intravenous Fluids, LOS: Length of Stay, MAP: Mean Arterial Pressure, NE: Norepinephrine, SOFA: Sequential Organ Failure Assessment, SSC: Surviving Sepsis Campaign.

Keywords: Mean arterial pressure; Mortality; Norepinephrine therapy; Sepsis; Septic shock, Sepsis; Survival

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1. INTRODUCTION

Septic shock presents one of the toughest challenges in critical care medicine. Its annual incidence continues to rise globally, with mortality rates ranging from 25% to 50% among the affected. Patients experiencing septic shock can be recognized by a clinical definition of sepsis coupled with onset of hypotension that necessitates the use of vasopressors to sustain a mean arterial pressure (MAP) of at least 65 mmHg and a serum lactate level exceeding 2 mmol/L (18 mg/dL) despite receiving sufficient volume resuscitation.[1]

Septic shock has a complex pathophysiology, which includes significant vasodilatation, cardiac dysfunction, relative and/or absolute hypovolemia, elevated metabolic demands, and changes in regional and microvascular perfusion. In addition to the effects of hypovolemia, the reduction in vascular tone is a significant factor that leads to hypotension observed in septic shock. This imbalance exacerbates the clinical picture by impairing hemodynamics and systemic vascular resistance.[2]

The 2023 Surviving Sepsis Campaign (SSC) Bundle emphasizes the prompt initiation of broad-spectrum antibiotics in sepsis management. In cases of hypotension or serum lactate levels ≥ 4 mmol/L, it recommends rapid crystalloid fluids to be administered at a rate of 30 mL/kg. Additionally, for hypotension unresponsive to initial fluid resuscitation, the guidelines suggest the use of vasopressors, with norepinephrine (NE) as the preferred agent, to achieve and maintain a target mean arterial pressure (MAP) of ≥ 65 mmHg.[3]

NE primarily exerts its effects through alpha-1 adrenergic receptor activation, leading to vasoconstriction. It also improves heart contractility at high doses by acting as an inotropic agent. Furthermore, NE's effect on beta-adrenergic receptors causes coronary artery dilatation. NE injection has been demonstrated to improve cardiac output and preload in individuals with potentially fatal hypotension. Additionally, a cohort study examining patients, who underwent resuscitation for septic shock, indicated a mortality benefit associated with the use of NE.[4]

The sensible use of different vasopressors in clinical context is the main focus of the current literature. The timing of vasopressor treatment, however, is becoming a crucial consideration that may be even more important than the agent selection. Notably, the best time to administer NE has not been sufficiently investigated in the literature, with varying definitions of "early" (from less than two hours to six hours after the onset of shock) and contradictory findings about its effects on organ dysfunction and mortality.[1,5,6] Bai et al.[7] showed better hemodynamics with NE started within 2 hours, whereas Ospina-Tascón et al.[8] found no advantage in mortality when comparing initiation within one hour vs. later. A crucial information gap is highlighted by these disparities: can extremely early NE treatment (less than two hours) offer any unique benefits versus delayed use?

By carefully contrasting the results of early (< 2 hours) and late (≥ 2 hours) NE administration, this study seeks to eliminate these doubts and provide evidence-based guidelines for the NE administration septic shock.

2. METHODOLOGY

This study was a prospective, double-blind, randomized trial involving 200 adult patients (≥ 18 years) who were admitted to the ICU at Ain Shams University with septic shock, based on criteria outlined by the International Sepsis Definitions Conference. The diagnostic criteria included sepsis-induced persistent hypotension characterized by a systolic blood pressure (SBP) of less than 90 mmHg, a decrease of at least 20% in SBP from the baseline, a mean arterial pressure (MAP) of less than 65 mmHg, and a serum lactate level exceeding 2 mmol/L.[9] Patients with a prior history of heart failure, known allergy to NE, or those who declined to participate in the study were excluded from the trial.

Utilizing the PASS 15 software for sample size determination, with a power threshold set at 80% and an α-error of 0.05, it was calculated that a sample size of 100 patients per group is required to identify a statistically significant difference in mortality rates between the two cohorts. Particularly, the mortality rate was 28.6% in the group who received NE early and 47.4% in the group that received it late.[10]

Participants in the study were randomized through a computer-generated sequence, with allocation concealed within sealed opaque envelopes to ensure bias reduction. The outcome assessors and patients were both blinded to the treatment groups. The cohort was divided into two groups: Group A and B. Group A included 100 patients who received prompt resuscitation, characterized by the simultaneous administration of crystalloid fluids (target

volume of 30 ml/kg) and NE infusion at an initial dose of 5 µg/kg/min via a central line, initiated immediately upon ICU transfer and within 2 hours of septic shock onset. Conversely, Group B comprised 100 patients who underwent fluid resuscitation with crystalloid fluids (targeting 30 ml/kg) post-ICU transfer, while NE infusion was initiated later, after a minimum of 2 hours following the onset of septic shock, also via central line.

All patients underwent comprehensive history taking, conducted with input from the patient and/or family members. Vital signs such as blood pressure, temperature, heart rate, and respiratory rate were carefully documented upon admission. Furthermore, sepsis indicators, the Body Mass Index (BMI), and the Sequential Organ Failure Assessment (SOFA) score were evaluated. Laboratory analyses included a complete blood count (CBC), coagulation profile (comprising prothrombin time, partial thromboplastin time, and international normalized ratio), renal function tests (urea and creatinine levels), and hepatic function tests (alanine transaminase and aspartate aminotransferase levels). Additionally, pan culture surveillance was performed to identify the causative organisms. Inflammatory markers such as C-reactive protein (CRP) and serum lactate levels were measured. Hemodynamic monitoring was rigorously applied, documenting parameters including SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), temperature (°C), central venous pressure (CVP), and urinary output (UOP).

Informed consent was obtained from all participants or their guardians prior to the initiation of the study. The research was evaluatively approved by the Institutional Review Board at the Faculty of Medicine, Ain Shams University (Protocol Record FMASU MS20/2024), and it was conducted in accordance with the principles outlined in the Declaration of Helsinki

The primary endpoint of the study is short-term mortality, encompassing hospital mortality as well as 28-day and 30-day mortality rates. Secondary endpoints are focused on various clinical metrics, including length of

Supplementary Table 1: Demographic characteristics and SOFA score

Parameter		Group A (n = 100)	Group B (n = 100)	Test value	P-value
Gender	Male	62 (62)	55 (55)	X^2 = 1.009	0.315
	Female	38 (38)	45 (45)		
Age	Mean ± SD	56.2 ± 10.65	57.6 ± 12.62	t = 0.830	0.408
	Range	34 - 70	33 – 72		
BMI	Mean ± SD	25.7 ± 4.83	27.2 ± 4.75	t = 1.321	0.197
	Range	20.3 – 31.2	21.4 – 33.8		
SOFA score	Median (IQR)	10 (10-13)	12 (10-14)	1.151	0.250
	Range	8 - 13	9 – 14		
Hemoglobin (g/dL)	Mean ± SD	9.7 ± 1.04	9.1 ± 1.5	1.654	0.095
	Range	8.8 – 12.2	8.5 – 12		
Hematocrit (%)	Mean ± SD	30.8 ± 4.83	29.1 ± 4.21	1.878	0.062
	Range	25.9 – 35.4	25.5 – 36.4		
RBC (10^3/µL)	Mean ± SD	3.5 ± 0.4	3.1 ± 0.3	0.790	0.448
	Range	3 - 4	2.6 – 3.7		
WBC (10^3/µL)	Mean ± SD	17.9 ± 3.6	18.5 ± 4.2	1.421	0.157
	Range	12 – 20	13 – 22		
PLT (10^3/µL)	Mean ± SD	82.6 ± 11.4	80.8 ± 10.2	0.273	0.785
	Range	72 – 100	70 – 97		

*Using: t-Independent Sample t-test for Mean ± SD; X2 = Chi-Square test, Mann Whitney test for median and Inter quartile range, P > 0.05 is insignificant; *P < 0.05 is significant; **P < 0.01 is highly significant.*

Table 1: Laboratory investigations during ICU stay

Lab report		Group A (n = 100)	Group B (n = 100)	Test value	P-value
Hemoglobin (g/dL)	Mean ± SD	9.7 ± 1.04	9.1 ± 1.5	1.654	0.095
	Range	8.8 – 12.2	8.5 – 12		
Hematocrit (%)	Mean ± SD	30.8 ± 4.83	29.1 ± 4.21	1.878	0.062
	Range	25.9 – 35.4	25.5 – 36.4		
RBC (10^3/µL)	Mean ± SD	3.5 ± 0.4	3.1 ± 0.3	0.790	0.448
	Range	3 - 4	2.6 – 3.7		
WBC (10^3/µL)	Mean ± SD	17.9 ± 3.6	18.5 ± 4.2	1.421	0.157
	Range	12 – 20	13 – 22		
PLT (10^3/µL)	Mean ± SD	82.6 ± 11.4	80.8 ± 10.2	0.273	0.785
	Range	72 – 100	70 – 97		
Creatinine (umol/L)	Mean ± SD	82.6 ± 32.82	131.9 ± 37.45	t = 1.987	0.050*
	Range	59.35 – 181.4	86.6 – 185.9		
ALT (U/L)	Mean ± SD	22.8 ± 11.52	21.1 ± 9.64	t = 0.198	0.845
	Range	10.0 – 40.2	13.4 – 35.7		
AST (U/L)	Mean ± SD	35.6 ± 15.74	39.9 ± 18.62	t = 0.379	0.658
	Range	20.5 – 73.0	22.2 – 68.0		
CRP (mg/L)	Mean ± SD	128.3 ± 36.24	141.1 ± 34.82	t = 2.056	0.041*
	Range	79 – 219	97 – 225		
Serum lactate (mmol/L)	Mean ± SD	4.4 ± 1.4	5.0 ± 1.7	t = 2.234	0.011*
	Range	3 – 6	4 - 7		
Culture	Positive	74 74	81 81	X^2 = 1.136	0.364
	Negative	26 26	19 19		

*Using: t-Independent Sample t-test for Mean ± SD; X2 = Chi-Square test, Mann Whitney test for median and Inter quartile range; *P < 0.05 is significant; **P < 0.01 is highly significant.*

stay in the ICU and hospital, total dosage of NE administered, time taken to reach the target mean arterial pressure (MAP) of ≥ 65 mmHg, volume of intravenous fluids administered at 6 and 24 hours post-admission, serum lactate levels, and the overall duration of NE treatment.

2.1. Statistical analysis

Recorded data were analyzed using SPSS version 23.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables were reported as means ± standard deviations and ranges for parametric distributions. For non-parametric data, medians with interquartile ranges (IQR) were utilized. Percentages and counts were used to express the qualitative variables. Normality of the data was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests.

3. RESULTS

Regarding the demographic profile of the study cohort, both groups were similar, and there was no difference that was statistically significant. The median SOFA score in Group A (early NE) was 10 (IQR: 10-13), while in Group B (late NE), it was 12 (IQR: 10-14). The absence of a significant change (P = 0.250) indicates that the level of organ dysfunction was comparable at baseline. Because of this constancy in SOFA ratings, baseline variations in the degree of organ failure are

unlikely to have an impact on the observed differences in outcomes. (Supplementary table 1)

Regarding laboratory findings, hemoglobin, and hematocrit levels are slightly higher in Group A but not significantly different from Group B. Despite minor variations, none of the complete blood picture parameters exhibit statistically significant distinctions between the groups (P > 0.05). (Table 1)

Group B demonstrated higher mean creatinine levels (131.9 ± 37.45 µmol/L) compared to Group A (82.6 ± 32.82 µmol/L), reaching borderline significance (P = 0.050). This suggests that delayed NE administration may exacerbate renal dysfunction, potentially due to prolonged hypotension and suboptimal perfusion. (Table 1)

Table 2: Comparison of hemodynamic profile during ICU stay

	Group A (n = 100)	Group B (n = 100)	Test value	P-value
SBP (mmHg)	92.6 ± 8.64	86.6 ± 7.68	2.687	0.000**
	81 – 100	78 – 100		
DBP (mmHg)	67.3 ± 8.92	64.2 ± 9.64	2.741	0.000**
	56 – 73	54 – 75		
MAP (mmHg)	62.4 ± 4.41	60.6 ± 3.46	1.438	0.122
	60 – 70	60 – 70		
HR (Beats/min)	84.6 ± 6.4	81.8 ± 7.8	1.951	0.050*
	69 – 92	67 – 90		
RR (Breath/min)	22.0 ± 3.0	23.0 ± 2.0	1.982	0.048*
	19 - 25	21 – 25		
Temperature (C°)	38.2 ± 0.12	38.4 ± 0.26	0.389	0.621
	38.0 – 38.4	38.2 – 38.6		
CVP (cmH_2O)	8.6 ± 1.54	7.8 ± 1.89	1.698	0.091
	5 – 12	5 – 11		
UOP (ml/Kg/h)	0.6 ± 0.14	0.5 ± 0.15	0.891	0.428
	0.5 – 0.8	0.4 – 0.7		

*Using: t-Independent Sample t-test for Mean ± SD and range; P > 0.05 is insignificant; *P < 0.05 is significant; **P < 0.01 is highly significant.. HR heart rate, RR respiratory rate, SBP (systolic blood pressure), DBP (diastolic blood pressure), and MAP (mean arterial pressure), CVP central venous pressure, UOP urinary output*

Group B's mean CRP levels were noticeably higher (141.1 ± 34.82 mg/L) than in Group A (128.3 ± 36.24 mg/L; P = 0.041), reflecting a heightened systemic inflammatory response in the late NE group. (Table 1)

Group B had significantly higher serum lactate levels (5.0 ± 1.7 mmol/L) than Group A (4.4 ± 1.4 mmol/L; P = 0.011). Elevated Lactate in Group B suggests delayed resolution of tissue hypoperfusion and shock. (Table 1)

For the hemodynamic Outcomes, Group A had significantly higher systolic blood pressure (92.6 ± 8.64 mmHg) and DBP (67.3 ± 8.92 mmHg) compared to Group B (86.6 ± 7.68 mmHg and 64.2 ± 9.64 mmHg, respectively; P < 0.01 for both). (Table 2)

Group A exhibited slightly higher heart rate (84.6 ± 6.4 beats/min vs. 81.8 ± 7.8 beats/min; P = 0.050) and respiratory rate (22.0 ± 3.0 breaths/min vs. 23.0 ± 2.0 breaths/min; P = 0.048). (Table 2)

As for the primary outcome, Group B had a significantly higher 28-30 days mortality rate (46%) than Group A (28%; P = 0.008). This underscores the critical impact of timely NE initiation on patient survival. (Table 3)

While secondary outcomes varied: time to achieve target MAP: Group A achieved MAP ≥ 65 mmHg significantly faster (1.0 ± 0.5 days) than Group B (1.5 ± 0.4 days; P < 0.01), volume of intravenous fluids (IVF): Group A received significantly less fluid at 6 hours (3.1 ± 0.9 L vs. 3.3 ± 0.8 L; P = 0.018) and 24 hours (6.2 ± 0.6 L vs. 6.9 ± 0.7 L; P < 0.01). Lactate clearance was markedly better in Group A (40.7% vs. 14.8%; P < 0.01), reflecting improved perfusion and metabolic recovery. Group A required a lower mean dose of NE (29.4 ± 9.7 mg vs. 32.8 ± 10.0 mg; P < 0.01) and a shorter duration of administration (2.6 ± 0.6 days vs. 2.9 ± 1.0 days; P = 0.038). Paradoxically, Group A had a more extended hospital LOS (12.5 ± 8.5 days) than Group B (11.0 ± 6.0 days; P = 0.003). This may reflect extended recovery times for survivors in Group A (Table 3).

Table 3: Primary and secondary outcomes

Outcome measures	Group A (n = 100)	Group B (n = 100)	Test value	P-value
28-30 day mortality	28 (28%)	46 (46%)	6.950	0.008*
Hospital Length (day)	12.5 ± 8.5	11.0 ± 6.0	3.003	0.003*
	5.75 – 28.75	5 – 19		
Time to achieve target MAP (≥ 65 mmHg) (day)	1.0 ± 0.5	1.5 ± 0.4	7.799	0.001**
	0.95 – 2	1 – 2		
Volume of intravenous fluids (at 6 h) (L)	3.1 ± 0.9	3.3 ± 0.8	2.394	0.018*
	2.2 – 4.0	2.5 – 4.0		
Volume of intravenous fluids (at 24 h) (L)	6.2 ± 0.6	6.9 ± 0.7	6.799	0.001**
	5.5 – 6.9	6.1 – 7.7		
Serum lactate clearance (%)	40.7 ± 28.6	14.8 ± 42.8	4.761	0.001**
	13.4 – 55.2	-33.2 – 45.6		
24-hr norepinephrine (mg)	29.4 ± 9.7	32.8 ± 10.0	3.558	0.001**
	20.0 – 30.0	30.0 – 43.0		
Duration of norepinephrine (days)	2.6 ± 0.6	2.9 ± 1.0	2.185	0.038*
	1.8 – 3.4	1.8 – 4		

*Using: t-Independent Sample t-test for Mean ± SD; X2 = Chi-Square test, Mann Whitney test for median and Inter quartile range, P > 0.05 is insignificant; *P < 0.05 is significant; **P < 0.01 is highly significant.*

4. DISCUSSION

Sepsis is a critical condition characterized by organ dysfunction resulting from an inappropriate response of the host to an infection. Individuals experiencing septic shock can be recognized by persistent low blood pressure necessitating vasoactive drugs to sustain a MAP of at least 65 mmHg, along with a serum lactate concentration exceeding 2 mmol/L, even after sufficient fluid resuscitation.[11,12]

Early recognition of the signs and prompt action especially within the first few hours of septic shock can significantly improve survival rates and recovery outcomes. A critical component of treatment is fluid resuscitation, which is often regarded as the first and most essential step in stabilizing patients and giving them a better chance of survival.[13,14] However, in the majority of septic shock patients, peripheral perfusion pressure cannot be raised by fluid resuscitation alone. Overload of extracellular fluid can also result in tissue edema and a higher death rate.[15,16] The early administration of vasoactive agents is essential for achieving hemodynamic stabilization in the management of septic shock.[17]

As an α1 and β1 adrenergic agonist, NE efficiently improves myocardial contractility and vascular tone. NE is recommended as the main vasopressor for treating septic shock in recent clinical guidelines. However, it seems that the choice of particular medications is less important in determining patient outcomes than the time of vasopressor delivery.[18,19] Multiple studies have indicated that the early initiation of NE in patients experiencing septic shock may be correlated with improved survival outcomes.[20,21]

The time between septic shock and NE onset is debatable. Though each research defines early NE differently, ranging from 2 to 6 hours or even longer. In addition, the influence of the timing of NE administration on other clinical outcomes of patients with septic shock, including as duration of hospital stay, mechanical ventilation time, and organ function, remains uncertain.[1,6]

Group A's significantly lower 28-30 days mortality rate (28% vs. 46%, P = 0.008) highlights the life-saving potential of early NE initiation. Early NE may mitigate the prolonged hypotension and tissue hypoperfusion that predispose patients to multi-organ failure and subsequent mortality. This aligns with prior studies demonstrating a survival advantage with early

vasopressor use. Along with our results, Li et al. reported a statistically significant difference between early and late NE groups regarding 28-day mortality, which was significantly higher in the late NE group, p = 0.045.[10] In addition, Ospina-Tascón et al. reported a statistically significant difference between early and late NE groups regarding mortality of 28 days, which was significantly higher in the delayed group.[8] Similarly, Elbouhy et al. reported that the in-hospital survival rate in the early NE group was 71.9% (41 patients) compared to 45.5% (20 patients) in the late group (P = 0.007).[22]

The faster time to achieve target MAP (≥ 65 mmHg) in Group A (1.0 days vs. 1.5 days, P < 0.01) underscores the efficacy of early NE in stabilizing hemodynamics. Better serum lactate clearance (40.7% vs. 14.8%; P < 0.01) reflects improved perfusion and metabolic recovery. These findings emphasize the dual role of NE in restoring vascular tone and optimizing tissue oxygenation. These findings are consistent with those of Li et al., who reported that there was a statistically significant difference between early and late NE groups regarding time to achieve target mean arterial pressure ≥ 65 mmHg, which was significantly longer in the late NE group, P = 0.01 and 6-hour lactate clearance.[10]

In the present study, our results showed that SBP and DBP differ significantly between the groups (P < 0.01), with Group A exhibiting higher mean values for both parameters. Mean arterial pressure shows no significant difference. Heart and respiratory rates display slight but significant differences (P < 0.05), with Group A having higher mean values for both. Temperature, central venous pressure, and urine output exhibit no significant differences between the groups.

These results matched Elbouhy et al.'s results, who argued that there was no statistically significant distinction between the studied groups regarding MAP, temperature, and CVP. Otherwise, they noted no statistically significant difference between the studied groups in SBP, DBP, HR, and RR.[22] Also, Ospina-Tascón et al. reported no significant difference between MAP and CVP in the early and late NE groups. Otherwise, they noted that there was no significant difference between early and late NE groups regarding SBP, DBP, HR, and RR.[8]

However, the Early-NE group had substantially higher mean arterial pressures than the Late-NE group at 1, 2, 4, and 6 hours following the start of septic shock, according to Bai et al.[7]

Group B exhibited higher creatinine and CRP levels, suggesting more significant renal impairment and systemic inflammation with delayed NE. These findings demonstrate the possible safeguarding benefits of early NE on renal function and inflammatory modulation, likely mediated by more efficient restoration of perfusion.

The reduced IVF requirements in Group A at 6 and 24 hours (P < 0.05) suggest that early NE reduces fluid dependency, mitigating the risks of fluid overload, including pulmonary edema and interstitial organ congestion. This is consistent with the findings of Li and colleagues, as there was a statistically significant difference between early and late NE groups regarding 24-hour infusion volume.[10]

The paradoxical finding of longer LOS in Group A warrants exploration. It may reflect extended recovery and rehabilitation periods for survivors, as opposed to the higher early mortality observed in Group B. This emphasizes the need for a nuanced interpretation of LOS as a metric of success in critical care. Li and co-workers showed no statistically significant difference between early and late NE groups regarding hospital length of stay. (10) Conversely, Ospina-Tascón et al. reported no statistically significant difference between early and late NE groups regarding the length of stay.[8]

Despite having a higher survival rate, Group A's lengthier hospital length of stay reflects survivor bias. Critically ill patients were disproportionately removed from the cohort in Group B due to more significant deaths (46%), which artificially shortened the average length of stay. Conversely, Group A's survivors may have required extended hospitalization for rehabilitation, management of sepsis-related complications (e.g., critical illness polyneuropathy), or treatment of secondary infections—a phenomenon well-documented in critical care trials.[23] This interpretation aligns with Li et al.,[10] who similarly observed no LOS difference after adjusting for mortality. Future studies should employ competing-risks regression to disentangle LOS from mortality effects.

In the present study, the administration of NE over 24 hours differs significantly between the groups (P < 0.01), with Group B receiving a higher mean dose (32.8 ± 10.0 mg) compared to Group A (29.4 ± 9.7 mg). The duration of NE administration also differs significantly (P < 0.05), with Group B receiving treatment for a longer mean duration (2.9 ± 1.0 days) compared to Group A (2.6 ± 0.6 days). These outcomes align with the findings of Bai et al., who reported that NE administration was significantly shorter, and that the quantity of NE administered in 24 hours was considerably less for the Early-NE group than the Late-NE group.[7] Ospina-Tascón et al. reported no statistically significant difference between early and late NE groups regarding NE max dose.[8]

The survival and hemodynamic advantages observed in Group A may be attributed to several pathophysiological

mechanisms. Early NE administration likely mitigates the vicious cycle of hypotension-induced tissue hypoperfusion, which exacerbates endothelial dysfunction, lactic acidosis, and mitochondrial failure.[11,12] By promptly restoring vascular tone through α1-adrenergic receptor activation, NE augments systemic vascular resistance, thereby improving coronary and cerebral perfusion pressures.[4,18] As seen by lower CRP levels in Group A, this early stabilization might reduce ischemic organ damage and the systemic inflammatory response. Moreover, pulmonary edema and abdominal compartment syndrome risks may be reduced through early mean arterial pressure (MAP) optimization, which may minimize the need for aggressive fluid resuscitation.[15,16] These mechanisms collectively contribute to faster lactate clearance and reduced multi-organ dysfunction.

5. LIMITATIONS

The single-center design may limit generalizability to other healthcare settings. Although adequately powered for primary outcomes, multi-center studies with a larger sample size may be required for more granular subgroup analyses (e.g., comorbid conditions, infection source). Secondly, survivor bias may have influenced secondary outcomes such as LOS.

Future multicenter studies should explore the interplay between NE timing and other vasopressors, long-term functional outcomes and quality of life in survivors, and cost-effectiveness analyses of early NE administration protocols.

6. CONCLUSION

The results of our study highlight how crucial it is to enhance hemodynamic recovery and survival in sepsis and septic chock, by including early vasopressor medication into standard care procedures. The observed anomaly in hospital length of stay highlights the significance of survivor-adjusted analysis in future research, even though it should be interpreted with caution.

7. Data availability

The numerical data generated during this research is available with the authors, and can be viewed on a reasonable request.

8. Conflict of interest

All authors declare that there was no conflict of interest.

9. Funding

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

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