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Original Research Article

Combination Therapy with Norepinephrine and Esmolol in Septic Shock: A Clinical and Prognostic Evaluation

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Abstract:

Background: Septic shock is a life-threatening condition characterized by circulatory failure, tissue hypoperfusion, and multiorgan dysfunction. While norepinephrine remains the first-line vasopressor to maintain mean arterial pressure, its persistent adrenergic stimulation often results in tachycardia and increased myocardial oxygen demand. Esmolol, a short-acting β1-selective blocker, has shown potential in reducing heart rate and improving cardiovascular efficiency in septic patients without compromising perfusion.

Aim: To evaluate the clinical effects and prognostic impact of norepinephrine combined with esmolol therapy in patients with septic shock admitted to the ICU.

Methods: This observational study was conducted over one year at Mata Gujri Memorial Medical College, Kishanganj, Bihar. A total of 25 patients with septic shock were included. Patients received standard septic shock management including fluid resuscitation, antibiotics, and norepinephrine. Esmolol was initiated for persistent tachycardia (>95 bpm) and titrated as per clinical response. Hemodynamic parameters, vasopressor dosage, lactate levels, SOFA score, and 28-day mortality were recorded. Data were analyzed using SPSS version 23.0.

Results: The mean baseline heart rate decreased significantly from 112.8 ± 10.4 bpm to 89.6 ± 9.1 bpm ($p < 0.001$) after esmolol administration, with MAP remaining stable. Norepinephrine dosage reduced from 0.35 ± 0.1 to 0.18 ± 0.07 μg/kg/min ($p < 0.01$). Lactate levels declined from 4.6 ± 1.3 to 2.9 ± 0.8 mmol/L ($p < 0.01$), and SOFA scores improved from 8.5 to 6.3 ($p < 0.05$). The 28-day survival rate was 72%. No significant adverse cardiac events were observed.

Conclusion: The combination of norepinephrine and esmolol in septic shock patients was associated with improved heart rate control, reduced vasopressor requirements, better lactate clearance, and favorable short-term outcomes. Esmolol was well tolerated and did not lead to hypotension or bradycardia in the studied population.

Recommendations: Esmolol may be considered as an adjunct therapy in septic shock patients with persistent tachycardia after adequate resuscitation. Larger randomized controlled trials are warranted to confirm these findings and establish standardized dosing protocols.

Keywords: Septic Shock, Esmolol, Norepinephrine, Heart Rate Control, Prognosis.

Introduction

Septic shock remains a major cause of mortality in (ICUs) worldwide, characterized by persistent hypotension, inadequate tissue perfusion, and multi-organ dysfunction despite adequate fluid resuscitation and vasopressor therapy [1]. The cornerstone of hemodynamic management in septic shock involves fluid resuscitation followed by vasopressor support, most commonly with norepinephrine, to maintain adequate mean arterial pressure (MAP) [2]. However, excessive adrenergic stimulation associated with prolonged catecholamine use may lead to tachyarrhythmias,

increased myocardial oxygen demand, and worsened outcomes [3].

Tachycardia is frequently encountered in septic patients and has been independently associated with higher mortality and prolonged ICU stay [4]. While norepinephrine effectively improves perfusion pressure, it does not address the elevated heart rate that can contribute to cardiac dysfunction. In this context, selective β1-blockade with **esmolol**, an ultra-short-acting β-blocker, has emerged as a novel adjunctive therapy. Esmolol reduces heart rate without significantly affecting blood pressure or cardiac output when used judiciously [5]. A growing body of evidence suggests that modulating the heart rate in septic shock may attenuate myocardial oxygen consumption, improve left ventricular filling, and enhance organ perfusion [6].

The landmark study by Morelli et al. in 2013 initially demonstrated the safety and potential benefit of esmolol in septic shock, showing reduced heart rate, improved stroke volume, and lower 28-day mortality [7]. Building upon this, several recent trials and meta-analyses have revisited the role of β-blockade in septic shock with more refined protocols and patient selection criteria. A 2020 meta-analysis by Sanfilippo et al. reaffirmed that esmolol use was associated with reduced mortality and vasopressor requirements without increasing adverse events [8]. Similarly, clinical evaluations in Asian ICUs reported improved lactate clearance and SOFA scores with esmolol therapy [9].

Despite these encouraging findings, β-blocker use in sepsis is still viewed cautiously due to concerns over potential hypotension and cardiac depression, especially in unstable patients. Therefore, further observational studies are warranted to validate its safety and effectiveness in real-world clinical settings. The present study aims to assess the clinical impact and prognostic implications of norepinephrine combined with esmolol therapy in patients with septic shock, focusing on hemodynamic parameters, vasopressor dependency, organ dysfunction, and short-term survival outcomes.

Methodology

Study Design: This study was designed as a hospital-based, observational study.

Study Setting: The study was conducted in the Intensive Care Unit (ICU) of Mata Gujri Memorial Medical College and Hospital, Kishanganj, Bihar. All procedures were carried out in accordance with institutional protocols and ethical guidelines.

Study Duration: The study was carried out over a period of one year, from July 2024 to June 2025. Data were collected continuously during this period as eligible patients were admitted and treated.

Participants: A total of 25 patients diagnosed with septic shock and requiring vasopressor support were included in the study. All patients received standard therapy for septic shock, including fluid resuscitation and antibiotics, with additional treatment using norepinephrine and esmolol as per protocol.

Inclusion Criteria

- Adult patients aged 18 years or older.
- Diagnosed with septic shock according to Sepsis-3 criteria.
- Requiring norepinephrine for hemodynamic support.
- Able to provide informed consent or through legal representative.
- No contraindication to β-blocker use.

Exclusion Criteria

- Patients with pre-existing bradycardia (heart rate <50 bpm).
- History of severe heart block or sick sinus syndrome.
- Pregnant or lactating women.
- Known allergy or intolerance to esmolol
- Patients with terminal illness not expected to survive 24 hours.
- Refusal to participate in the study.

Bias Control: To minimize selection bias, consecutive sampling was used, enrolling all eligible patients during the study period. Observer bias was minimized by ensuring that outcome assessments were performed by physicians blinded to the study's objectives. Data entry and analysis were carried out by individuals not directly involved in patient care.

Data Collection: Data were collected using a structured case record form. Baseline demographic details, clinical history, vital parameters, laboratory values, hemodynamic status, vasopressor dosage, esmolol titration details, and outcome measures such as 28-day mortality, length of ICU stay, and organ dysfunction were recorded. All patient records were anonymized before analysis.

Procedure: All enrolled patients received standard treatment for septic shock including fluid resuscitation, antibiotics, and norepinephrine titration to maintain mean arterial pressure ≥65 mmHg. Esmolol was initiated in patients with persistent tachycardia (heart rate >95 bpm) after adequate volume resuscitation and was titrated based on heart rate and hemodynamic stability. Hemodynamic parameters and vasopressor requirements were monitored at 6-hour intervals.

Treatment duration and response were documented over the ICU stay

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 23.0. Descriptive statistics such as mean, (SD), and percentage were used to summarize the data. Continuous variables were compared using the Student's t-test or Mann–Whitney U test depending on normality of distribution. Categorical variables were analyzed using the Chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.

Results

A total of 25 patients with septic shock were included in the study. The mean age of the participants was 57.2 ± 11.6 years, with 15 (60%) males and 10 (40%) females. The most common source of infection was pneumonia (36%), followed by urinary tract infection (24%), intra-abdominal sepsis (20%), and others (20%).

Table 1: Baseline Demographic and Clinical Characteristics (n = 25)

Characteristic	Value
Age (mean ± SD)	57.2 ± 11.6 years
Sex (Male/Female)	15 (60%) / 10 (40%)
Mean Arterial Pressure (MAP)	62.5 ± 5.2 mmHg
Heart Rate (baseline)	112.8 ± 10.4 bpm
Serum Lactate (mmol/L)	4.6 ± 1.3
SOFA Score (mean)	8.5 ± 2.4
Source of Infection	
- Pneumonia	9 (36%)
- Urinary tract infection	6 (24%)
- Intra-abdominal sepsis	5 (20%)
- Others (e.g., cellulitis, CLABSI)	5 (20%)

Hemodynamic Response: After esmolol administration, there was a significant reduction in heart rate from 112.8 ± 10.4 bpm to 89.6 ± 9.1 bpm ($p < 0.001$) without a significant drop in MAP, which remained stable at 64.3 ± 4.7 mmHg ($p = 0.09$). The requirement for norepinephrine was reduced significantly within 24 hours.

Table 2: Hemodynamic Parameters Before and After Esmolol Administration

Parameter	Before Esmolol	After 24 hrs of Esmolol	p-value
Heart Rate (bpm)	112.8 ± 10.4	89.6 ± 9.1	<0.001
MAP (mmHg)	62.5 ± 5.2	64.3 ± 4.7	0.09
Norepinephrine dose (µg/kg/min)	0.35 ± 0.1	0.18 ± 0.07	<0.01

Organ Dysfunction and Lactate Clearance: Patients showed an improvement in organ perfusion, as indicated by a significant decrease in serum lactate levels from 4.6 ± 1.3 to 2.9 ± 0.8 mmol/L ($p < 0.01$) after 48 hours. The SOFA score improved from 8.5 ± 2.4 to 6.3 ± 1.9 ($p < 0.05$) over the same period.

Clinical Outcomes: Out of 25 patients, 18 (72%) survived the 28-day follow-up period. The mortality rate was 28% (7 patients). The mean ICU stay was 8.1 ± 3.5 days for survivors, whereas non-survivors had a significantly shorter ICU stay of 5.2 ± 2.1 days due to early deterioration.

Table 3: Outcome Measures

Outcome Measure	Value
28-day Mortality Rate	7 (28%)
28-day Survival Rate	18 (72%)
ICU Length of Stay (mean ± SD)	7.2 ± 3.4 days
SOFA Score Improvement	From 8.5 → 6.3 ($p < 0.05$)
Lactate Clearance (%)	36.9%
Need for Mechanical Ventilation	16 (64%)
Ventilator-free Days (median)	12 (IQR: 9–16)

Adverse Events: No major bradycardia (<50 bpm) or severe hypotension was noted. Two patients required temporary discontinuation of esmolol due to borderline hypotension, which resolved with fluid optimization. No arrhythmias or allergic reactions were observed.

Discussion

In this observational study involving 25 patients with septic shock, the combination therapy of norepinephrine and esmolol demonstrated favorable clinical and hemodynamic outcomes. The average age of participants was 57.2 years, with a slight male predominance. Pneumonia emerged as the most common underlying infection. Baseline parameters revealed elevated heart rates and serum lactate levels, consistent with the hyperdynamic state of septic shock.

After administration of esmolol in addition to norepinephrine, patients showed a statistically significant reduction in heart rate, from a mean of 112.8 to 89.6 bpm ($p < 0.001$), without compromising mean arterial pressure (MAP), which remained stable ($p = 0.09$). This indicates that esmolol effectively controlled tachycardia without causing hemodynamic instability. Importantly, norepinephrine requirements decreased significantly within the first 24 hours ($p < 0.01$), suggesting improved cardiovascular efficiency and reduced vasopressor dependence.

In terms of organ function, there was a notable decline in serum lactate levels and a reduction in SOFA scores over 48 hours (from 8.5 to 6.3, $p < 0.05$), indicating better tissue perfusion and multiorgan recovery. These improvements are clinically meaningful, given that persistent tachycardia and high lactate levels are associated with poor outcomes in septic shock.

Out of the 25 patients, 18 survived (72%) and 7 (28%) succumbed during the 28-day follow-up period. Survivors had longer ICU stays but showed more pronounced hemodynamic and metabolic stabilization. The lower mortality and improved organ function parameters support the potential prognostic benefit of early β-blockade in carefully selected patients with septic shock.

Adverse effects were minimal; no significant bradycardia or arrhythmias were reported. Only two patients required temporary discontinuation of esmolol due to borderline hypotension, which was manageable with fluid resuscitation. The safety profile observed here further reinforces the clinical utility of esmolol in septic shock.

Combination therapy involving norepinephrine and esmolol has been increasingly investigated in septic shock due to its potential to control tachycardia and improve cardiovascular stability. A 2024 clinical study involving 96 patients demonstrated that adding esmolol to norepinephrine improved cardiac function, suppressed inflammatory markers, enhanced oxygenation, and improved patient prognosis without significantly increasing adverse drug reactions [10].

Randomized controlled trials have further explored esmolol's benefits in septic shock. One study showed that although esmolol did not significantly reduce vasopressor requirements or hasten shock reversal, it did lead to lower C-reactive protein levels and reduced oxygen consumption, suggesting anti-inflammatory and metabolic benefits [11]. Another randomized trial revealed that esmolol reduced heart rate consistently over 7 days, although it did not impact overall mortality, norepinephrine dosage, or organ dysfunction scores [12].

Meta-analyses have provided broader evidence. A comprehensive 2023 meta-analysis found that esmolol significantly reduced overall mortality (RR 0.65) and heart rate, with no significant effects on lactate levels or mean arterial pressure (MAP), suggesting cardiovascular benefit without compromising perfusion [13]. Similarly, another meta-analysis concluded that esmolol use in sepsis significantly improved survival and lowered biomarkers of myocardial injury (troponin I and CK-MB) while having minimal effect on MAP and central venous pressure [14]. A third meta-analysis also confirmed decreased 28-day mortality and better heart rate control, though with no significant improvement in ICU stay or inflammatory cytokines [15].

In a 2025 pilot randomized study, early administration of esmolol post-resuscitation was feasible and led to faster heart rate reduction without compromising hemodynamic stability, even though a slight early drop in cardiac index was observed [16]. Another feasibility study in the U.S. supported similar findings, showing that esmolol was well-tolerated and all patients survived to 90 days [17].

Animal studies reinforced these outcomes. In porcine models, esmolol significantly improved heart rate variability and arterial function, suggesting beneficial autonomic modulation in septic shock [18]. Another study comparing esmolol to ivabradine showed that only esmolol maintained cardiac autonomic improvements when norepinephrine was administered, highlighting its compatibility with vasopressors [19].

Finally, in a clinical study examining esmolol's cardioprotective effects, esmolol improved myocardial diastolic function and lowered biomarkers of cardiac stress, without negatively impacting tissue perfusion or oxygen metabolism [20].

Conclusion

In conclusion, the findings suggest that norepinephrine–esmolol combination therapy is effective in controlling heart rate, reducing vasopressor need, enhancing perfusion, and

possibly improving survival outcomes in patients with septic shock. Although the sample size is limited, the results are promising and warrant further investigation in larger controlled trials.

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