# Early Versus Late Norepinephrine Therapy in Management of Septic Shock as Prognostic Factor of Mortality

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**Abstract: Background:** Sepsis is a clinical syndrome of life-threatening organ dysfunction caused by a dysregulated response to infection. In septic shock, there is a critical reduction in tissue perfusion; acute failure of multiple organs, including the lungs, kidneys, and liver. Common causes include many different species of gram-positive and gram-negative bacteria. Immunocompromised patients may have uncommon bacterial or fungal species as a cause. Signs include fever, hypotension, oliguria, and confusion. Diagnosis is primarily clinical combined with culture results. Early recognition and treatment is critical. Treatment is aggressive fluid resuscitation, antibiotics, surgical excision of infected or necrotic tissue and drainage of pus, and supportive care. **Objective:** Demonstration of the relationship between delay in initiation of vasopressor therapy (norepiniphrine) in the management of septic shock patients and the mortality rate. Determine effects of early Norepinphrine adminstration on septic shock patients and their ICU length of stay. **Methodology:** This study was conducted on 50 diagnosed patients with septic shock at general intensive care unit Ain Shams University Hospitals. Patients are divided into two groups according to time (Hours) to initial norepinephrine administration: group A (Early-NE group which received norepinephrine <3 hours after the onset of septic shock) and group B (Late-NE group which received norepinephrine ≥3 hours after the onset of septic shock). **Results:** The mean arterial pressure improvement is better in the Early-NE group than in the Late-NE group during the first 12 hours of resuscitation and the subsequent serum lactate levels were significantly lower in the Early-NE group than in the Late-NE group during the first 24 hours of resuscitation. There was no significant difference between the two groups in the ICU Length of Stay. 28 Day Mortality was significantly lower in group A than in group B. The overall 28-day mortality was 40 %. Every one hour delay in norepinephrine initiation within the first six hours after the onset of septic shock is associated with increase in mortality rate by 10,66%. The 28-day mortality was 24% in the Early-NE group A and 56% in the Late-NE group B. **Conclusion:** This study indicates that early administration of norepinephrine for septic shock is associated with improved survival. Mortality increases when initial norepinephrine administration is delayed.

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**Keywords:** Norepinephrine, Septic Shock

## 1. Introduction:

Sepsis is a clinical syndrome of life-threatening organ dysfunction caused by a dysregulated response to infection. In septic shock, there is a critical reduction in tissue perfusion; acute failure of multiple organs, including the lungs, kidneys, and liver. Common causes include many different species of gram-positive and gram-negative bacteria. Immunocompromised patients may have uncommon bacterial or fungal species as a cause. Signs include fever, hypotension, oliguria, and confusion. Diagnosis is primarily clinical combined with culture results. Early recognition and treatment is critical. Treatment is aggressive fluid resuscitation, antibiotics, surgical excision of infected or necrotic tissue and drainage of pus, and supportive care **(Singer et al., 2016).**

Early goal-directed therapy provided significant benefits with respect to outcomes for septicshock patients. However, massive fluid resuscitation may increase extravascular edema, aggravate pulmonary dysfunction and compromise tissue oxygenation. Therefore, investigating the rational use of vasopressors in septic shock is very important. Thus far, most studies have focused on the rational use of different types of vasopressors **(Daley et al.,2013).**

The third edition of the guidelines for management of severe sepsis and septic shock alsoconcentrates on the choice of vasopressors. The guidelines recommend that vasopressors (norepinephrine as the first choice) be administered for hypotension refractory to initial fluid resuscitation and to maintain a mean arterial pressure (MAP) ≥65 mm Hg **(Dellinger et al.,2012).** However, it is the timing of vasopressor therapy, rather than the specific agent, that appears to be crucial **(Parrillo et al., 2008).**

Aim of the work:

Demonstration of the relationship between delay in initiation of vasopressor therapy (norepiniphrine) in the management of septic shock patients and the mortality rate. Determine effects of early Norepinphrine administration on septic shock patients and their ICU length of stay.

Patients and Methods:

- **Type of Study:** prospective controlled study.
- **Study Setting:** General intensive care unitAin Shams University Hospitals.
- **Study Population:** After obtaining approval from the institutional ethics committee**,** fifty patients with septic shock meeting the following selection criteria was included in this study.

**Inclusion Criteria**

Patients with septic shock with tissue hypoperfusion as oliguria or altered consous level with age at least 18 years after receiving resuscitating fluid as 30ml/kg and initiating vasopressor therapy (norepiniphrine).

**Exclusion Criteria:**

1- Concomitant uncontrolled hemorrhage.
2- Concomitant cardiogenic shock.
3- Patients who died in first 24 hours after onset of septic shock.

- **Study Tools:**

The study was done on adult patients at least 18 years old with diagnosis of septic shock as described by SSC. With persistent hypotension despite adequate fluid resuscitation 30 ml/kg crystalloid fluid. Then determine mortality rate in the two groups of study who receive norepiniphrine in first three hour and after three hours. The following data was collected:

Age, Gender, MAP, the Acute Physiology and Chronic Health Evaluation (APACHE) II scores based on the worst values obtained within 24 hours after the onset of septic shock, Microbiologic results, Primary infection sites, Total amount of intravenous fluid (L) adminstered within 6hours after the onset of septic shock, time hours to initial anti microbial treatment, corticosteroid treatment, norepiniphrine duration, lactate level, ICU Length of Stay and 28 day mortality.

**Statistical Analysis:**

Statistical presentation and analysis of the present study was conducted, using Mean, Standard Deviation, Student t-test [Unpaired] and chi-square tests by (*IBM SPSS* (Statistical Package for the Social Sciences) *Version 20.0. Armonk, NY: IBM Corp.)*. Unpaired Student T-test was used to compare between tow groups in quantitative data and chi-square used to compare between tow groups in qualitative data.>0.05 Non significant <0.05* significant <0.001** High significant.

**3. Results:**

This study was conducted on 50 diagnosed patients with septic shock. Patients are divided into two groups according to time (Hours) to initial norepinephrine administration: group A (Early-**NE** group which received norepinephrine <3 hours after the onset of septic shock) and group B (Late-NE group which received norepinephrine ≥3 hours after the onset of septic shock).

**Table (1): Demographic data and baseline characteristics:**

| | **Group A (n=25)** | **Group B (n=25)** | **P-value** |
|---|---|---|---|
| **Gender** | | | |
| Female | 10(48%) | 9(64%) | 0.771 |
| Male | 15(52%) | 16(36%) | |
| **Age (years)** | 54.72±6.31 | 56.09±5.48 | 0.416 |
| **APACHE II score** | 18.14±3.07 | 16.87±2.75 | 0.130 |
| **Cultures positive results** | 22(88%) | 20(80%) | 0.440 |
| **Primary infection site** | | | |
| Skin and soft tissue | 4(16%) | 5(20%) | 0.713 |
| Intra-abdominal | 5(20%) | 6(24%) | 0.733 |
| Urinary tract | 2(8%) | 1(4%) | 0.552 |
| Respiratory | 10(40%) | 12(48%) | 0.569 |
| Intravascular catheter | 4(16%) | 1(4%) | 0.157 |

There were no significant differences between group A and B with respect to age, gender, positive cultures results, the primary infection sites and APACHE II scores.

**Table (2): Therapeutic intervention and secondary outcomes**

| | Group A (n=25) | Group B (n=25) | P-value |
|---|---|---|---|
| **Time to initial antimicrobial treatment (hr)** | 1.42±0.45 | 1.36±0.67 | 0.712 |
| **Total amount of iv fluids administered in the First 6hrs (L)** | 3.08±0.52 | 4.2±0.65 | <0.001** |
| **Need for administration of iv corticosteroid** | 16 (64%) | 20(80%) | 0.208 |
| **Norepinephrine Duration (days)** | 2.35±0.51 | 3.5±0.72 | <0.001** |

There was no significant difference between the two groups in the time to initial antimicrobial treatment and the Need for administration of iv corticosteroid. The Norepinephrine Duration was shorter in group A than in group B. The Total amount of iv fluids administered in the First 6hrs (L) in group B was more than group A.

**Changes of MAP and serum lactate level in monitoring the Early-NE group A and the Late-NE Tgroup B.**

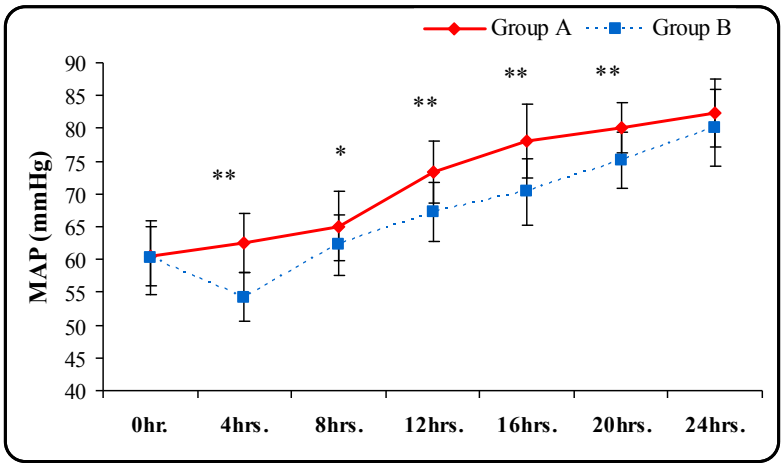


**Figure (1): Mean arterial pressure was higher at 4,8,12,16,20and24 hours after the onset of septic shock in group A than in group B.**

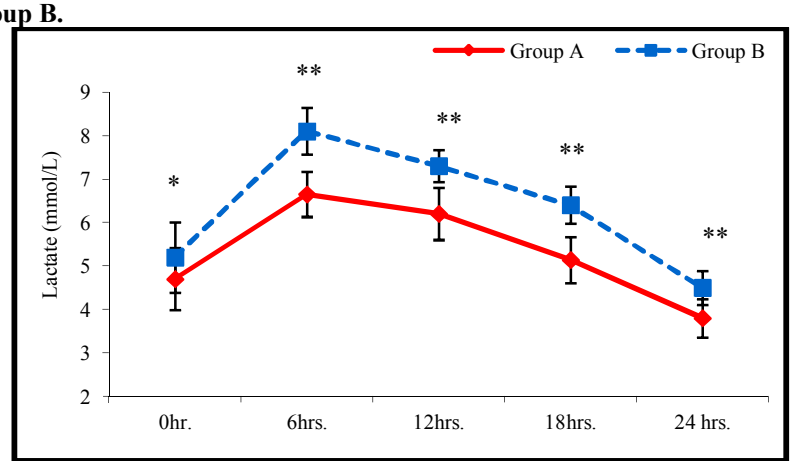


**Fig. (2): Serum lactate levels at six, twelve, eighteen and twenty four hours after the onset of septic shock were significantly lower in the Early-NE group A than in the Late-NE group B.**

**Table (3): Primary outcome:**

| | Group A (n=25) | Group B (n=25) | P-value |
|---|---|---|---|
| **ICU Length of Stay (days)** | 10.2 ±5.2 | 11.4±5.4 | 0.427 |
| **28 Day Mortality** | 6 (24%) | 14(56%) | 0.021* |

There was no significant difference between the two groups in the ICU Length of Stay. 28 Day Mortality was significantly lower in group A than in group B.

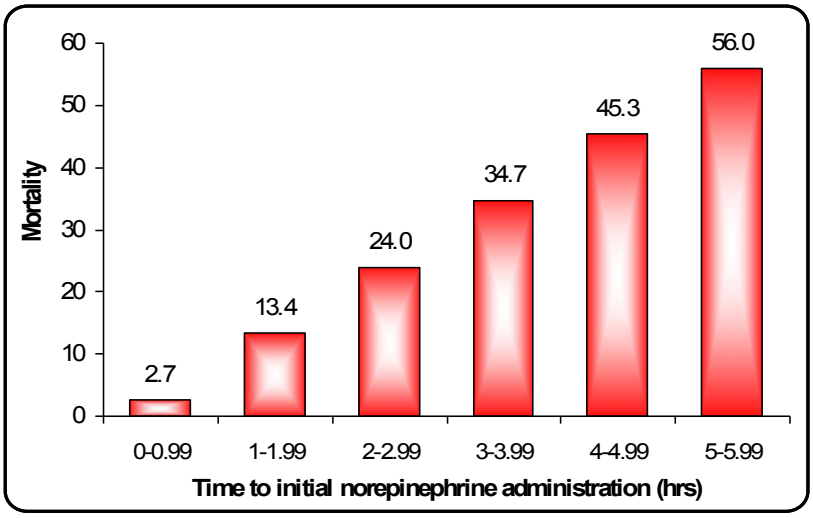


**Fig. (3): Mortality of patients whose initial norepinephrine administrations were within the indicated time interval.**

The 28-day mortality was 24% in the Early-NE group A and 56% in the Late-NE group B. Every one hour delay in initiation of norepinephrine therapy was associated with increase in mortality rate by 10,66%.

**4. Discussion:**

The present data show that the time from the onset of septic shock to initial norepinephrine administration is an important determinant of survival. The risk of death was significantly increased with delay in norepinephrine initiation after the onset of septic shock. For every one hour delay in norepinephrine initiation within the first six hours from the onset of septic shock, the mortality increased by 10,66%. This could not be attributed to the increase of severity of septic shock in the delayed norepinephrine initiation group as both groups were comparable in the initial assessment of sepsis scoring by APACHE II score with no significant difference ($p > 0.05$). Initial blood pressure values were similar in both groups, but patients in the Early-NE group had lower initial serum lactate levels than those in the Late-NE group. Early norepinephrine administration reduced the duration of norepinephrine treatment significantly and shortened the duration of shock with less intravenous fluid requirements.

According to the SSC guidelines 2012 fluids and antimicrobials should be administered as early as possible in patients with septic shock, but the optimal timing of vasopressor administration was less clear, so the patients with septic shock were recommended to receive vasopressors early or late depend on the patient's response to initial fluid resuscitation and the judgment of the physicians. It remains difficult to determine if late administration of norepinephrine reflects a poor evaluation of the disease severity of the patient and if the higher mortality is related to a globally less appropriate management of the patients ***(Dellinger et al., 2012).***

In our study, the included 50 patients suffering from septic shock received norepinephrine as the initial vasopressor agent. The overall 28-day mortality was 40 %. Every one hour delay in norepinephrine initiation within the first six hours after the onset of septic shock is associated with increase in mortality rate by 10,66%.

The 28-day mortality was significantly lower in the Early-NE group (<3hrs) 24% compared to 56% in the Late-NE group (≥3 hours). *Xiaowuet al.* showed different results with overall 28-day mortality 37.6% and the 28-day mortality was 29.1% in the Early-NE group (within two hours) and 43.3% in the Late-NE group (after two hours). Every 1-hour delay in norepinephrine initiation during the first 6 hours after septic shock onset was associated with a 5.3% increase in mortality ***(Xiaowu et al., 2014 ).***

The difference of results may be due to larger sample size of patients included (213 patients). Our study was prospective controlled randomized study while other study was retrospective observational. Also the time was different as Early-NE group (within two hours) and the Late-NE group (after two hours).

The Xiaowuet al. study has an important limitation as being retrospective trial design limited their ability to identify precisely the causes for delay in initial vasopressor administration and to determine a

causal relationship between the delay in norepinephrine administration and the septic-shock mortality. ***(Xiaowu et al., 2014 ).***

The percentage of patients with positive cultures was 84 % in our study compared to around 62% in *Xiaowuet al. study*. Some factors may have influenced these results. First, our ICUs were general surgical ICUs and most patients admitted to them had severe nosocomial respiratory infections. Second, most patients in our study underwent multiple surgical interventions which would increase the opportunity for pathogens to enter the blood.

In a retrospective study, *Morimatsu et al.* reported that survival of septic shock patients treated with early and exclusive norepinephrine administration (median time 1.3 hours) compared favorably with that predicted by severity scores ***(Morimatsu et al., 2004).***

In rats with septic shock, Sennoun et al. compared the effects of early versus delayed norepinephrine administration, and showed that the mesenteric/aortic blood flow ratio was higher and blood lactate concentrations lower in an early compared to a late norepinephrine group ***(Sennoun et al., 2007).***

In another retrospective study, *Subramanian et al.* found that liberal vasopressor use was not associated with less progression to organ failure in septic shock. However, the volume of fluids received within six hours was significantly greater in the liberal than in the conservative group and they used different types of vasopressors, including dopamine, phenylephrine, norepinephrine and vasopressin. Their study was also conducted in a medical ICU, so that differences in patient characteristics may have influenced the results as well ***(Subramanian et al., 2008).***

In our study showed that the Total amount of iv fluids administered in the First 6hrs (L) was significantly larger in the Late-NE group (≥3 hours) than in the Early-NE group (<3hrs) ($p < 0.05$ ). The Norepinephrine duration (days) was shorter in the Early-NE group (2.35±0.51 d) than in the Late-NE group (3.5±0.72 d) ($p < 0.05$ ). The mean arterial pressure improvement is better in the Early-NE group than in the Late-NE group during the first 12 hours of resuscitation and the subsequent serum lactate levels were significantly lower in the Early-NE group than in the Late-NE group during the first 24 hours of resuscitation ($p < 0.05$).

In our study the blood pressure in the late-NE group was maintained by more intravenous fluid resuscitation than in the Early-NE group therefore norepinephrine thrapy was delayed in the Late-NE group.

Sennoun et al. reported that early norepinephrine administration spared approximately 30% of the fluid volume required in the late or non-norepinephrine groups. ***(Sennoun et al., 2007).***

Septic shock is characterized by hypotension, related in part to absolute and relative hypovolemia. The former is the result of vascular leakage caused by endothelial injury and the latter is the result of systemic vasodilation. In addition, sepsis can result in down-regulation of norepinephrine receptors. Increased MAP with norepinephrine may improve organ perfusion and this may result in lower serum lactate levels. Therefore, expedited norepinephrine administration can be a rational approach to rapidly restore organ perfusion. One may, therefore, be recommended to initiate norepinephrine administration simultaneously with fluid resuscitation at the onset of septic shock. Obviously, this strategy should not prevent adequate fluid resuscitation, as one must pay attention to a so-called 'vasoconstrictor-masked hypovolemia' ***(Hinder et al., 2003).***

This study indicates that early administration of norepinephrine for septic shock is associated with improved survival. Mortality increases when initial norepinephrine administration is delayed.

Our study confirmed the results of Hour-1 Bundle in the Surviving Sepsis Campaign update 2018 that included**:** Urgent restoration of an adequate perfusion pressure to the vital organs is a key part of resuscitation. This should not be delayed. If blood pressure is not restored after initial fluid resuscitation, then vasopressors should be commenced within the first hour to achieve mean arterial pressure (MAP) of≥ 65 mm Hg ***(Levy et al., 2018).***

Conclusion:

This study indicates that early administration of norepinephrine for septic shock is associated with improved survival. Mortality increases when initial norepinephrine administration is delayed. Early norepinephrine initiation can increase MAP, shorten the duration of hypotension and, thereby, may improve vital organ perfusion and decrease serum lactate levels. These data suggest that more prompt and aggressive norepinephrine administration should be considered as part of initial resuscitation therapy for septic shock.

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