Original Article

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Comparison of Earlier vs Early Start of Norepinephrine in Patients with Septic Shock

Qudsia Rasool[1], Rana Imran Sikander[2], Syed Muneeb Ali[3], Suresh Kumar[4], Farah Naz[5], Muhammad Haroon Anwar[6]

[1]Senior Registrar, [2]Professor, [3,5]Assistant Professor, [4]Associate Professor, [6]Postgraduate trainee, Department of Anesthesia and Critical Care Medicine, Pakistan Institute of Medical Sciences, Islamabad

Author`s Contribution

[1,2,6]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Data Collection.
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Address of Correspondent
Dr. Muhammad Haroon Anwar
Postgraduate trainee
Department of Anesthesia and Critical Care Medicine, Pakistan Institute of Medical Sciences, Islamabad
haroonanwar22@gmail.com

ABSTRACT

Objective: To compare the effects of earlier Nor-epinephrine administration i.e. within 40 minutes of initial fluid administration with early Nor-epinephrine administration i.e. 80 minutes of fluid administration in terms of time required to achieve mean arterial pressure of greater 65 mm of Hg and volume of resuscitation fluid administered.

Methodology: This single blind randomized control trial was carried out at Department of Anesthesia and Critical Care Medicine from 1st January 2023-31st December 2023. Patients fulfilling the inclusion criteria i.e. age >18 years having septic shock with Mean arterial pressure of less than 65 mm of Hg requiring fluid resuscitation with vasopressor therapy were enrolled in the study and divided into two groups using computer generated random numbers. Group E patients received Nor-epinephrine infusion at 80 minutes while those belonging to group EL received Nor-epinephrine infusion at 40 minutes after initial fluid administration.

Results: Patients who received EL achieved MAP greater than equal to 65mm Hg earlier with median time of 60 minutes as compared to 80 minutes in group E with p value of 0.000. The median volume administered was significantly lower in group EL that was 2000 ml as compared to 2600 ml in group E with p value of 0.000.

Conclusion: Earlier administration of Nor-epinephrine results in restoration of MAP of 65 mm Hg and requires less amount of crystalloid fluid during volume resuscitation which can improve outcomes for patients with septic shock.

Keywords: Septic shock, Fluid Resuscitation, Nor-epinephrine.

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Introduction

Sepsis is a life-threatening condition characterized by multi-organ dysfunction occurring due to dysregulated inflammatory response in the host.[1] A mortality of 32.8% was observed among adult patients admitted to intensive care units in UK[2] A mortality of 36.6% was observed at national level which is higher in those patients presenting with septic shock.[3] Septic shock is a form of distributive shock characterized increased vascular permeability, loss of fluid in the third space causing tissue edema, depletion in intravascular volume, hypotension and tachycardia.[4] The shock causes hypoperfusion of the end organs resulting in their dysfunction and increases the morbidity and mortality. Therefore, treatment of shock is of the prime importance. It begins with fluid resuscitation typically administering up to 80ml/kg of crystalloid fluid as a bolus through adequate intravascular access.[4] Vasopressors are added as per need to improve tissue perfusion and limit overzealous fluid administration which can have a number of side effects such as tissue edema, impaired tissue oxygenation leading to worsening of tissue dysfunction, electrolyte and acid base abnormalities and volume overload.[5] These side effects can lead to increased mortality. Therefore, early use of Nor-epinephrine is recommended in management of patients with septic shock. The timing of Nor-epinephrine is important so that outcomes can be improved. In a study done, administration of Norepinephrine at 25 minutes as compared to late administration of Nor-epinephrine at

120 minutes resulted in cause earlier restoration of blood pressure, better lactate clearance and improve in-hospital survival.[6] Mean arterial pressure of 65 mm of Hg was achieved at 1h as compared to 2h while comparing early vs late nor epinephrine administration.[6] It was also noted that patients in the early group received significantly lower volume of fluids i.e. 25 mL/kg vs. 32.5 mL/kg in the late groups.[6] Early administration of Nor-epinephrine was also recommended for patients with septic shock who are more likely to suffer from adverse effects of fluid resuscitation such as those with acute respiratory distress syndrome.[7] Similarly, Norepinephrine initiation within the first 3 h of presentation, regardless of blood pressure dependency on preload was found to be associated with longer survival time and shorter duration of vasopressor and invasive positive pressure mechanical ventilation requirement.[8] Therefore, it is clear that optimal timing of Nor-epinephrine is still controversial and varies across different literatures. Therefore, further studies are required to determine the optimal timing of Nor-epinephrine administration so that formal guidelines can be made.

Methodology

This randomized control trial was carried out Department of Critical Care Medicine at Pakistan Institute of Medical Sciences from 1st January 2023-31st December 2023.

An ethical approval was taken before starting this study. An informed consent was taken before enrolling the participants. Patients fulfilling the inclusion criteria i.e. age >18 years having septic shock with Mean arterial pressure of less than 65 mm of Hg requiring fluid resuscitation with vasopressor therapy. Patients having acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, active arrythmias, gastrointestinal hemorrhage, pregnancy, seizures, drug intoxication, burn injury, trauma and requirement for immediate surgery and advance stage malignancy were excluded from the study. After enrolling the patients, they were divided into two groups using computer generated random numbers with group E patients received Nor-epinephrine infusion at 80 minutes while those belonging to group EL received Nor-epinephrine infusion at 40 minutes after initial fluid administration. Time required to achieve mean arterial pressure of greater than 65 mm of Hg was noted as well as volume of fluid administered for resuscitation was also noted. Baseline hemodynamic parameters and parameters across different time frames were also noted.

Results

Data was entered on SPSS version 26.0. and analyzed. The distribution of gender was similar across two groups. In group E, 66.67% of the participants were male while rest were female. In group EL, 63.33% were male while rest were female. The difference was insignificant with p value of 0.71. The demographic profile and baseline hemodynamics were comparable across two groups as shown in the table I.

Patients of group EL required less time to reach MAP ≥ 65 mm Hg and considerably required less fluid volume. A comparison is shown in the table II.

Table I: Comparison of age and baseline hemodynamics across two groups.

	Group E Mean ± SD	**Group EL Mean ± SD**	**P value**
Age	44.27 ± 9.02	40.17 ± 11.36	0.127
Baseline HR	107.73 ± 16.94	104.97 ± 13.49	0.487
Baseline SBP	74.73 ± 3.32	73.63 ±10.04	0.571
Baseline DBP	34.83 ±3.10	36.73 ±5.62	0.111
Baseline MAP	50.43 ±13.12	51.40 ±13.21	0.777

Table II: Comparison of outcome variables across two groups.

	Group E Median (IQR)	**Group EL Median (IQR)**	**P value (Mann Whitney U test)**
Time to reach MAP ≥ 65 mm Hg	80 (20)	60 (25)	0.000
Volume of fluid used in resuscitation	2600 (600)	2000 (300)	0.000

Discussion

The baseline hemodynamic profiles along with demographic variables were similar among two groups. Majority of the participants were male. The study revealed that earlier start of Nor-epinephrine among patients of septic shock at 40 minutes resulted earlier achievement of MAP ≥ 65 mm Hg. Time to achieve MAP of 65 mm of Hg when Nor-epinephrine was started at 40 minutes was 60 minutes while it was 80 minutes when Nor-epinephrine was started at 80 minutes. The difference was statistically significant with p value of 0.000. The timing of Nor-epinephrine administration was also found to be strongly associated with time when target mean arterial pressure is achieved. It was found that when Nor-epinephrine was administered in the pre-

hospital setting, MAP of 65 mm of Hg was achieved earlier and 30 day mortality was considerably low.[9] Similarly it was found that administration of Nor-epinephrine within 1st hour of fluid resuscitation results in MAP of 65 mm Hg within 1hour while those who received Nor-epinephrine after 1 hour the time to achieve MAP of 65 mm Hg was 1.5h with difference being statistically significant with p value of 0.010(10). As previously mentioned, our findings are similar to the results of above-mentioned study. Similarly MAP of 65 mm of Hg achieved earlier among patients who received Nor-epinephrine within 1 hour of fluid resuscitation than those receiving it late whit better mortality at 28 days.[11]

Earlier administration of Nor-epinephrine was associated with less amount of fluid required for resuscitation. The amount of fluid required for resuscitation among patients receiving earlier Nor-epinephrine was 2000ml while it was 2600ml among patients who received Nor-epinephrine later. This is again supported by a number of studies.[9,10,11] In recent systemic review of literature early administration of Nor-epinephrine as compared to late administration was associated with earlier achievement of MAP of 65 mm Hg and improves mortality.[1,2]

Furthermore earlier administration of Nor-epinephrine has been found to improve survival among patients of septic shock.[13] The overall mortality benefit can be due to earlier restoration of MAP of 65 mm Hg and less volume of crystalloid fluid infused. In septic shock patient microvasculature is leaky and crystalloid fluids administered are rapidly mobilized to extravascular compartments which can lead to tissue edema, impairing their oxygenation, exchange of materials with the nearby capillary beds and overall compromising their function.[14] Our study was limited as it did not assess the effects of earlier vs early administration of Nor-epinephrine on mortality, end organ function and microvasculature. Further larger studies are required before a definitive conclusion can be made.

Conclusion

Earlier administration of Nor-epinephrine results in restoration of MAP of 65 mm Hg and requires less amount of crystalloid fluid during volume resuscitation which can improve outcomes for patients with septic shock.

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