



### **Efficacy of Noradrenaline (Vasopressin) in Hemodynamic Stability of Blood Pressure in Septic Patients**

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#### **Abstract**

**Aims:** To study the efficacy of noradrenaline (Vaso press in) in hemo dynamic stability of blood pres sure in septic patients.

**Methods:** A total of 156 patients admitted to the emer gency medical unit of the Department of Emergency Medicine, KIMS Hospital, Anayara, Trivandrum were selected for this study from January 2017 to June 2017.

Patient demographic details, results of biological markers such as fever, decreased urine output, altered sensorium, pulse rate, systolic blood pressure, respiratory rate, pal lor, icterus, cyanosis, clubbing, oedema, HB, TLC, plate lets, TB, AST, ALT, TP, albumin, globulin, urea, creati nine, sodium, potassium, deranged LFT's, RFT's, altered mentation (GCS<15), and q SOFA Score (>2) details were collected and recorded.

Statistical significance was done using SPSS version 20.0. Frequencies were reported in percentages, the association between and before and after noradrenaline infusion was analyzed by Chi-square tests, and a p-value of <0.05 was considered statistically significant.

**Results:** Out of 156 septic patients males (50.6%) were higher than females (49.4%) and a higher number of patients were in the age group of <30 years. Smoking was found higher in the study of septic patients.

After noradrenaline infusion, 55.8% of the septic patient 's fever was recovered (Chi-square - 83.23, P-value - <0.001). After noradrenaline infusion 13.4%, and 9.6 % of septic patients showed a clinical boost in dis coloration of urine and generalized body swelling res pectively (Chi-square - 10.68, P-value - <0.001), (Chi-square - 3.586, P-value - <0.029).

After noradrenaline infusion 19.8%, and 20.6% of septic patients presented clinical improvement in decreased urine output and altered sensorium respectively (Chi-square - 13.67, P-value - <0.001) (Chi-square - 83.23 P-value - <0.001). After noradrenaline infusion 58.4%, and 89.7% of septic patients expressed clinical refinement in heart rate and low systolic blood respectively (Chi-square - 107.2, P-value - <0.001) (Chi-square - 250.3, P-value - <0.001). After noradrenaline infusion 28.9%, and 25% of septic patients outlined clinical improvement in respiratory rate and pallor respectively (Chi-square -

29.96, P-value - <0.001) (Chi-square - 20.95, P-value - <0.001).

After noradrenaline infusion 30.2%, and 23.1% of septic patients revealed clinical upgrades in icterus and cyanosis respectively (Chi-square - 32.02, P-value - <0.001) (Chi-square - 25.48, P-value - <0.001).

After noradrenaline infusion 28.9%, and 49.4% of patients indicated clinical rectification in clubbing and oedema respectively (Chi - square - 33.77, P-value - <0.001) (Chi-square - 27.13, P-value - <0.001). After Nora drenaline infusion 38.5%, and 53.2% of patients pro claimed clinical upswing in HB and TLC respectively (Chi-square - 46.222, P-value - <0.001) (Chi - square - 91.05, P-value - <0.001).

After noradrenaline infusion 38.5%, and 28.2% of patients exhibited clinical improve ment in platelets and TB respectively (Chi-square - 49.76, P-value - <0.001) (Chi-square - 29.13, P-value - <0.001). After Nora drena line infusion 46.8%, and 30.1% of patients showed clinical upgrading in AST and ALT respectively (Chi-square - 69.84, P-value - <0.001) (Chi - square - 35.21, P - value - <0.001).

After noradrenaline infusion 31.4%, and 36.5% of patients presented clinical advancement in TP and album in respectively (Chi-square - 37.25, P-value - <0.001) (Chi-square - 45.43, P-value - <0.001). After noradrena line infusion 8.9%, and 73% of patients showed-up clinical furtherance in globulin and urea respectively (Chi - square - 4.998, P-value - <0.025) (Chi-square - 166.6, P - value - <0.001).

After noradrenaline infusion 28.2%, and 23.1% of patients flaunted clinical enhancement in creatinine and sodium respectively (Chi-square - 28.8, P-value - <0.025) (Chi-square - 25.48, P-value - <0.001). After noradrena line infusion 8.9%, of patients showed clinical

improvement in potassium (Chi-square - 6.825, P-value - <0.009).

After noradrenaline infusion 70.5%, and 62.1% of pati ents displayed clinical improvement in deranged LFTs and RFTs respectively (Chi-square - 158.3, P-value - <0.001) (Chi-square - 122.1, P-value - <0.001). After noradrenaline infusion 91%, and 85.3% of patients showed clinical advancement in GCS<15 and q SOFA Score (>2) respectively (Chi-square - 257, P-value - <0.001) (Chi-square - 228.3, P-value - <0.001).

After noradrenaline infusion 80.1% of our study patient's blood pressure was normalized (Chi-square - 205.2, P-value - <0.001).

**Conclusions:** In conclusion, norepinephrine infusion in sepsis patients improves most of the biological markers, hence stabilizing the vital signs. Physicians, especially emergency clinicians, must meticulously observe the noradrena line infusion, and document all procedures, observations, and symptomatic improvements, to reduce mortality from septic shock.

**Keywords:** Noradrenaline, Blood Pressure (BP), Sepsis, Vaso pressin, quick Sequential Organ Failure Assessment (qSOFA), (Glasgow Coma Scale (GCS), De ranged LFTs, and RFTs.

### Introduction

Sepsis is one of the fatal stages of infectious diseases and occurs when an existing infection sets off a chain reaction throughout the body. Infections that cause sepsis usually begin in the lungs, urinary tract, skin, or gastro intestinal tract. Septic shock occurs when blood pressure drops below the normal level leading to the fatality of the septic patients. Abe, T et al described that the source of sepsis is very important, as the source of sepsis will aid in specific anti-microbial therapy and also will support the correct selection of sample collection<sup>1</sup>.

In sepsis patients, Nwafor, J. I et al describe that septic shock occurs when their Systolic Blood Pressure (SBP) reduces very low ( $\leq 90$  mm Hg) than the normal level (120mm Hg) for more than 1 hour<sup>2</sup>. Resuscitation or blood pressure can be increased to a normal level by infusion fluids such as inotropic medicines or Vaso pressors. Hamzaoui, O et al explains these fluids as the "magic potion" and these fluids increase the quantity of fluid in the blood and the blood flow in the vital organs thus increasing the blood pressure<sup>3</sup>.

For septic shock patient's infusion of noradrenaline or norepinephrine is provided and noradrenaline is an organic chemical that belongs to the family catecholamine and noradrenaline works on the brain as a Hormone and as well as a neurotransmitter. Mitra, A. K et al narrated that noradrenaline is the "social network button" of the body<sup>4</sup>.

Hernández et al reported that infusion of peripheral circulation of lactate circulation will increase the mortality rate in adult septic patients suffering from septic shock<sup>5</sup>. Permpikul, C et al explained that the Vaso pressor infusion is an urgent intervention required in patients with sepsis and septic shock patients, as per the author of this study, the timing of vasopressors initiation is unclear, and in their study norepinephrine administered at 0.05  $\mu\text{g}/\text{kg}/\text{min}$  in 1 hour with the onset of sepsis or septic shock<sup>6</sup>.

The other study published by Mamadjonov, N et al detailed that noradrenaline is one of the vasopressin that increases the systolic blood pressure in septic shock patients, and noradrenaline 0.08 mg/ml infusion must be administered intravenously or in the central vein through the catheter to reduce the tissue necrosis, and administration must be controlled rate with the aid of syringe piston pump. Do not use the peripheral vein for Noradrenaline infusion<sup>7</sup>.

Infusion of vasopressors or nor-adrenaline within the "golden time" is important and Kuttab, H. I et al expressed that in their study of 1032 patients with septic shock that the mortality rate increased in patients when the patient was administered 30 mL/kg within 3 hours after the septic shock onset (OR 1.52, 95%CI: 1.03–2.24), indicating that the within 3 hours is a long time to infuse noradrenaline to septic shock patients, hence infusing noradrenaline to septic shock patients lesser than 3 hours is required to reduce the mortality rate in them<sup>8</sup>.

Wardi, G et al study provides a recommendation of  $< 30$  mL/kg of initial fluid administration to septic shock patients improves the blood volume, leading to the improvements of hypoperfusion, thus increasing the BP, even though not several evidence-based studies are available for fluid infusion, the author also adds notes on infusion requires careful management of vital signs, treatment effects, and hemodynamics<sup>9</sup>.

In septic shock patients, when we infuse noradrenaline, we have to monitor vital markers along with several biological markers, among them cardiac monitoring very important vital marker needs monitoring, before and after infusion of noradrenaline. The low fluid quantity will be a measurement error, and the high quantity of fluid will be a risk by overload, thus recommended quantity will bring positive hemodynamics in the septic shock patients and improve their mortality rate<sup>10</sup>.

In septic shock patients, the management of respiratory markers is also as important as the management of heart rate, MacIntyre, N. R et al recommends that sufficient oxygen supply to the patient is important to bring the best positive hemodynamics, hence Non-Invasive Ventilation (NIV) support will bring the targeted SPO<sub>2</sub> in the septic patients who receive noradrenaline infusion<sup>11</sup>.

In septic shock patients, during infusion of noradrenaline, the other risk we need to manage is a new infection. New

infection with multi-drug resistant bacteria again will worsen the sepsis shock, hence during infection new infection must be prevented with infection control measures. Barrot, L et al reported that in their study, during fluid infusion, 2 sepsis patients suffered from a new infection<sup>12</sup>.

In sepsis, certain predictive markers can also be used to monitor the hemodynamics during fluid infusion, qSOFA score is one the predictive marker that can determine the utility of fluid, and positive hemodynamics, and can work as an alert system for the administration of Noradrenaline in septic shock patients<sup>13</sup>.

Deshpande, J. P et al study described the management of anesthesia in patients with sepsis, amputated patients, coagulation abnormalities, and patients with deranged LFTs, and RFTs due to neuraxial block<sup>14</sup>.

In septic shock patients, Thompson, K et al explained that along with the qSOFA score, deranged LFTs, RFTs, and GCS also support the quick and simple way of identifying sepsis, regardless of several screening methods, the improved outcome was presented by appropriate and timely treatment, and approaches with lesser delay<sup>15</sup>.

Rhee C et al declares that due to the lack of data on health facts that the quantity of vasopressin usage, usage of cardiovascular health issues, and requirement of antibiotics in septic shock patients<sup>16</sup>.

Hence, we have to have clear, evidence-based, multi-facet guidelines for the usage of vasopressin in hemodynamic stability of blood pressure in septic shock patients, accordingly, we have conducted this present study with the usage of noradrenaline infusion for increasing the blood pressure in septic shock patients, and provided the evidence-based data for other researchers, and clinicians for further development, and thus supporting in hemodynamic changes in the low blood pressure mortality rate in septic shock patients.

### **Ethical clearance**

This study was approved by the Institutional Review Board and permission to conduct the study was obtained.

### **Inclusion criteria**

- Patients with sepsis-induced hypotension. <90 mm Hg, MAP <60 or a fall of >40 mm Hg from baseline.
- Patients with hypoxemia: PaO<sub>2</sub> <72 mm Hg (9.47 kPa) at FiO<sub>2</sub> 0.21.

### **Exclusion criteria**

- Patients were unresponsive to fluid resuscitation.
- Patients with known pulmonary disease.

### **Materials and methods**

#### **Methodology**

#### **Study Subjects**

156 patients who met the inclusion criteria were selected to conduct this study at KIMS Hospital Emergency Department Emergency Medicine Unit, Anayala, Trivandrum, for 6 months from January 2017 to June 2017.

#### **Informed consent Form**

Informed consent was obtained from the patient's relatives before the cases were included in the study. Patient data were recorded in the proforma for data collection.

#### **Clinical History and Investigations**

In this observational study, patient demographics and investigations such as fever<sup>17</sup>, decreased urine output<sup>18</sup>, altered sensorium<sup>19</sup>, Pulse Rate (PR) (<60 to >100 beats/minute)<sup>20</sup>, Systolic blood pressure (SBP) (>120mm)<sup>21</sup>, Respiration Rate (RR) (<12 to >20 breaths/minute)<sup>22</sup>, pallor<sup>23</sup>, icterus<sup>24</sup>, Cyanosis<sup>25</sup>, Clubbing<sup>26</sup>, Oedema<sup>27</sup>, Hemoglobin (HB) – males - < 14 - >18 g/ dl, females - < 12 - > 16 g/ dl<sup>28</sup>, Total Leucocyte Count (TLC) <4,500 to > 11,000/ ml<sup>29</sup>, Platelets - < 150,000 to > 450,000 / μL<sup>30</sup>, Total Bilirubin (TB) >1.2mg/dL<sup>31</sup>, Aspartate transaminase (AST) <8->45 (U/L)<sup>32</sup>, Alanine transaminase (ALT) < 7->56 (U/L)<sup>33</sup>, Total Protein (TP) <6.0 to> 8.3

(g/dL)<sup>34</sup>, Albumin- <3.4 to >5.4 g/dL<sup>35</sup>, Globulin-< 2.0 to >3.5 (g /dL) <sup>36</sup>, Urea - <5 to >20 mg/ dl<sup>37</sup>, Creatinine - males - <0.7 to >1.3 (mg/dL), females- <0.5 to >1.1 (mg/dL) <sup>38</sup>, Sodium- <136 and >145 (mmol/L)<sup>39</sup>, Potassium-adults - <3.5 to >5.2 (mEq/L), children ages 1 to 18 years -<3.4 to >4.7 (mEq/L)<sup>40</sup>, Deranged LFT's<sup>41</sup>, Deranged RFT's<sup>42</sup>, Altered mentation (GCS<15)<sup>43</sup>, q SOFA Score > 2 (Sepsis)<sup>44</sup> were collected and recorded.

**Data collection**

30 mL/kg of noradrenaline was infused into the study patients within 3 hours after the septic shock onset, the study patient’s demographics and biological markers were collected twice before the administration of Nora drenaline infusion and after the administration of Nora drenaline infusion. The results were collected and record ed.

**Analysis**

The analysis was done to identify the efficacy of nor-adrenaline before and after administration in the study subjects. The analytical data were tabulated in the result section.

**Statistical Analysis**

This study data were analyzed using IBM SPSS 25.0 version 24. Clinical and biological markers associated with efficacy were assessed using chi-square and a P-value <0.05 was considered statistically significant.

**Results**

A total of 156 septic patients with lower blood pressure were included in this study, and data on the basic profile of septic shock patients with low blood pressure were provided in Table 1. Among them, males 79 (50.6%) were higher than females 77 (49.4%). Out of 156 study patients, 79 (50.6%) patients were in the age group of ≤ 30 years, 71 (45.5%) patients were in the age group of 31 - 60 years, and 6 (3.8%) patients were in the age group of > 60 years. In this study patient’s personal histories were

recorded, and out of 156 septic patients Tobacco Chew ing was found in 30 (19.2%) of patients, smoking was found in 32 (25.5%) of patients, and alcohol con sumption was found in 30 (19.2%) of patients.

Table 1: Basic Profile of Septic Patients with Low Blood Pressure

Variables	Categories	N (%)
Gender	Males	79(50.6)
	Females	77(49.4)
Age Categories (in years)	≤ 30 years	79 (50.6)
	31-60 years	71 (45.5)
	≥61 years	6 (3.8)
Personal History	Tobacco Chewing	30 (19.2)
	Smoking	32 (20.5)
	Alcohol	30 (19.2)

To study the hemodynamic changes that occur in the blood pressure in septic patients, we have infused noradrenaline as per the guidelines and recorded the clinical results before and after the administration of noradrenaline. Distribution of presenting complaints and general examination of septic patients before, and after administration of noradrenaline were recorded and presented in Table 2.

Among the presenting complaints recorded in the study patients, fever was present in 87 (55.8%) patients before the administration of noradrenaline and after the admini stration of noradrenaline, only 12 (7.7%) patients were with fever with statistical significance (Chi-square - 83. 23, P-value - <0.001). Loose tools and vomiting were present in 22 (14.1%) patients before the administration of Nora drenaline and after the administration of Nora drenaline, only 12 (7.7%) patients with loose tools, and vomiting (Table 2).

Yellowish discoloration of urine was present in 35 (22. 4%) patients before the administration of noradrenaline and after administration of noradrenaline, only 14 (9.0%)

patients with yellowish discoloration of urine with statistical significance (Chi-square - 10.68, P-value - <0.001). Generalized body swelling was present in 51 (32.7%) patients before administration of noradrenaline and after administration of noradrenaline, only 36 (23.1%) patients were with Generalized body swelling with statistical significance (Chi-square - 3.586, P-value - <0.029) (Table 2).

Decreased urine output was present in 69 (44.2%) patients before the administration of noradrenaline and after administration of noradrenaline, only 38 (24.4%) patients were with decreased urine output with statistical significance (Chi-square - 13.67, P-value - <0.001).

Altered sensorium was present in 60 (38.5%) patients before the administration of noradrenaline and after administration of noradrenaline, only 28 (17.9%) patients were with altered sensorium with statistical significance (Chi-square - 83.23, P-value - <0.001) (Table 2).

Among the general examination recorded in the study patients, abnormal pulse rate/ heart rate was present in 116 (74.4%) patients before the administration of Noradrenaline, and after administration of noradrenaline, only 25 (16.0%) patients were with abnormal pulse rate/heart rate with statistical significance (Chi-square - 107.2, P-value - <0.001).

Low Systolic Blood Pressure (LSBP) ( $\leq 90$  mm Hg) (Hypotension) was present in 156 (100%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 16 (10.3%) patients with low systolic blood pressure (Chi-square - 250.3, P-value - <0.001) (Table 2).

Abnormal respiration rate (RR) (<12 to >20 breaths/minute) was present in 72 (46.2%) patients before the administration of noradrenaline and after administration of noradrenaline, only 27 (17.3%) patients with abnormal respiration rate (RR) (<12 to >20 breaths/minute) with statistical significance (Chi-square - 29.96, P-value - <0.001). Pallor was present in 77 (49.4%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 38 (24.4%) patients with pallor (Chi-square - 20.95, P-value - <0.001) (Table 2).

Icterus was present in 75 (48.1%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 28 (17.9%) patients were with Icterus with statistical significance (Chi-square - 32.02, P-value - <0.001). Cyanosis was present in 50 (32.1%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 14 (9.0%) patients with cyanosis (Chi-square - 25.48, P-value - <0.001) (Table 2).

Clubbing was present in 63 (40.4%) patients before administration of noradrenaline and after administration of noradrenaline, only 18 (11.5%) patients were with clubbing with statistical significance (Chi-square - 33.77, P-value - <0.001). Oedema was present in 102 (65.4%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 56 (16.0%) patients with edema (Chi-square - 27.13, P-value - <0.001) (Table 2).

Table 2: Distribution of Presenting Complaints and General Examination of Septic Patients Before and After Administration of Noradrenaline

Variables	Categories	Before Administration of Noradrenaline infusion	After Administration of Noradrenaline infusion	Chi-square	P value
Presenting Complaints	Fever	87 (55.8)	12 (7.7)	83.23	<0.001*
	Loose stools & Vomiting	22 (14.1)	12 (7.7)	3.301	<0.069
	Yellowish Discoloration of Urine	35 (22.4)	14 (9.0)	10.68	<0.001*
	Generalized Body Swelling	51(32.7)	36 (23.1)	3.586	0.029*
	Decreased urine output	69 (44.2)	38 (24.4)	13.67	<0.001*
	Altered Sensorium	60 (38.5)	28 (17.9)	83.23	<0.001*
General Examination	Pulse Rate/ Heart Rate (<60 to >100 beats/minute)	116 (74.4)	25 (16.0)	107.2	<0.001*
	Low Systolic Blood Pressure (LSBP) (≤90 mm Hg)	156 (100)	16 (10.3)	250.3	<0.001*
	Respiration Rate (RR) (<12 to >20 breaths/minute)	72 (46.2)	27 (17.3)	29.96	<0.001*
	Pallor	77(49.4)	38 (24.4)	20.95	<0.001*
	Icterus	75 (48.1)	28 (17.9)	32.02	<0.001*
	Cyanosis	50 (32.1)	14 (9.0)	25.48	<0.001*
	Clubbing	63(40.4)	18 (11.5)	33.77	<0.001*
	Oedema	102 (65.4)	56 (16.0)	27.13	<0.001*

Distribution of biological markers including LFT and RFT of septic patients before and after administration of noradrenaline were recorded and plotted in Table 3. Among the biological markers tested for the study patients abnormal Hemoglobin (HB) (males-<14-> 18 g/dl, females -<12->16 g/dl) was present in 105 (67.3%) patients before administration of noradrenaline and after administration of noradrenaline, only 45 (28.8%) patients were with HB with statistical significance (Chi-square - 46.222, P-value - <0.001).

Abnormal Total Leucocyte Count (TLC) (<4,500 to > 11,000/ml) was present in 106 (67.9%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 23 (14.7%) patients were

with TLC with statistical significance (Chi-square - 91.05, P-value - <0.001). Abnormal Platelets (<150,000 to > 450,000/ μL) were present in 87 (55.8%) patients before the administration of noradrenaline and after administration of noradrenaline, only 27 (17.3%) patients with platelets with statistical significance (Chi-square - 49.76, P-value - <0.001) (Table 3).

Among the abnormal LFT found in the study patients, abnormal Total Bilirubin (TB) (>1.2mg/dL) was present in 70 (44.9%) patients before administration of Noradrenaline and after administration of noradrenaline, only 26 (16.7%) patients were with TB with statistical significance (Chi-square - 29.13, P-value - <0.001). Abnormal Aspartate transaminase (AST) (<8->45 (U/L) was present

in 103 (66.0%) patients before the administration of noradrenaline and after administration of noradrenaline, only 30 (19.2%) patients were with AST with statistical significance (Chi - square – 69.84, P-value - < 0.001) (Table 3).

In the tested LFT parameters, abnormal Alanine transaminase (ALT) (< 7->56 (U/ L) was present in 67 (42.9%) patients before administration of noradrenaline and after administration of noradrenaline, only 20 (12.8%) patients were with ALT with statistical significance (Chi-square - 35.21, P-value - <0.001).

Abnormal Total Protein (TP) (<6.0 to> 8.3 (g/ dL) was present in 70 (44.9%) patients before the administration of noradrenaline and after the administration of Noradrenaline, only 21 (13.5%) patients with TP with statistical significance (Chi-square - 37.25, P-value - <0.001) (Table 3).

Among the conducted LFT markers, abnormal Albumin (<3.4 to >5.4 g/dL) was present in 84 (53.8%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 27 (17.3%) patients were with albumin with statistical significance (Chi-square - 45.43, P-value - <0.001). Abnormal Globulin (< 2.0 to > 3.5 (g/dL) was present in 30 (19.2%) patients before the administration of noradrenaline and after administration of noradrenaline, only 16 (10.3%) patients

were with globulin with statistical significance (Chi-square - 4.998, P-value - <0.025) (Table 3).

We also have done RFT biological markers for this study patients and found abnormal Urea (<5 to >20 mg/dl) was present in 135 (86.5%) patients before administration of noradrenaline and after administration of noradrenaline, only 21 (13.5%) patients were with urea with statistical significance (Chi-square - 166.6, P-value - <0.001).

Abnormal Creatinine (males <0.7 to >1.3 (mg/dL), females <0.5 to >1.1 (mg/dL) was present in 71 (45.5%) patients before administration of noradrenaline and after administration of noradrenaline, only 27 (17.3%) patients were with creatinine with statistical significance (Chi-square - 28.8, P-value - <0.001) (Table 3).

Abnormal Sodium (<136 and >145 (mmol/L) was found in 50 (32.1%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 14 (9.0%) patients with sodium with statistical significance (Chi-square - 25.48, P-value - <0.001). Abnormal Potassium (adults <3.5 to >5.2 (mEq/L), children ages 1 to 18 years-<3.4 to >4.7 (mEq/L) was present in 23 (14.7%) patients before administration of noradrenaline and after administration of noradrenaline, only 9 (5.8%) patients were with potassium with statistical significance (Chi-square - 6.825, P-value - <0.009) (Table 3).

Table 3: Distribution of Bio logical Markers including LFT and RFT of Septic Patients Before and After Admini stration of Noradrenaline

Variables	Categories	Before Administration of Noradrenaline infusion	After Administration of Noradrenaline infusion	Chi-square	P value
Basic Profile of Lab Investigation	Hemoglobin (HB)-Males-<14->18 g/dl, Females-<12->16 g/dl	105 (67.3)	45 (28.8)	46.222	<0.001*
	Total Leucocyte Count (TLC) <4,500 to >11,000/ml	106 (67.9)	23 (14.7)	91.05	<0.001*
	Platelets-<150,000 to > 450,000/μL	87 (55.8)	27 (17.3)	49.76	<0.001*



Liver	Total Bilirubin (TB) (>1.2mg/ dL)	70 (44.9)	26 (16.7)	29.13	<0.001*
Function Tests (LFT)	Aspartate transaminase (AST) (< 8 ->45 (U/L)	103 (66.0)	30 (19.2)	69.84	<0.001*
	Alanine transaminase (ALT) (< 7->56 (U/L )	67 (42.9)	20 (12.8)	35.21	<0.001*
	Total Protein (TP) (<6.0 to> 8.3 (g/dL)	70 (44.9)	21 (13.5)	37.25	<0.001*
	Albumin (<3.4 to >5.4 g/dL)	84 (53.8)	27 (17.3)	45.43	<0.001*
	Globulin (< 2.0 to >3.5 (g/dL)	30 (19.2)	16 (10.3)	4.998	0.025*
Renal Function Test (RFT)	Urea (<5 to >20 mg/dl)	135 (86.5)	21 (13.5)	166.6	<0.001*
	Creatinine (Males-<0.7 to >1.3 (mg/dL), Females- <0.5 to >1.1 (mg/dL)	71 (45.5)	27(17.3)	28.8	<0.001*
	Sodium (<136 and >145 (mmol/L)	50 (32.1)	14 (9.0)	25.48	<0.001*
	Potassium-Adults (<3.5 to >5.2 (mEq/L), Children ages 1 to 18 years-<3.4 to >4.7 (mEq/L)	23 (14.7)	9(5.8)	6.825	0.009*

In this present study conducted in septic patients for the stability of blood pressure, we also analyzed the predictive markers, and outcome (increasing the blood pressure) before and after administration of noradrenaline, and the results were expressed in Table 4.

Deranged LFTs are the biological markers of LFT tests that show >1.5 times higher levels than normal levels.

Deranged LFTs were found in 144 (92.3%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 34 (21.8%) patients with deranged LFTs with statistical significance (Chi-square - 158.3, P-value - <0.001).

We also have done Deranged RFTs are the biological markers of RFT tests that shows >1.5 times higher level than normal level.

Deranged RFTs were found in 135 (86.5%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 38 (24.4%) of patients with deranged RFTs with statistical significance (Chi-square - 122.1, P-value - <0.001) (Table 4).

Altered mentation (Glasgow Coma Scale (GCS<15) is also one of the predictive markers analyzed in our study

and we found abnormal altered mentation GCS<15 in 156 (100%) patients before administration of noradrenaline and after administration of noradrenaline, only 14 (9.0%) patients were with altered mentation GCS<15 with statistical significance (Chi-square - 257, P-value - <0.001) (Table 4).

The other predictive markers q SOFA Score (>2) (sepsis) was analyzed and found abnormal q SOFA Score (>2) in 156 (100%) patients before administration of noradrenaline and after administration of noradrenaline, only 23 (14.7%) of patients were with q SOFA Score (>2) with statistical significance (Chi-square - 228.3, P-value - <0.001).

Along with the predictive markers we also analyzed the outcome of the study (stability of blood pressure) from lower BP, and we found low BP was in 156 (100%) patients before the administration of noradrenaline and after the administration of noradrenaline, only 31 (19.9%) of patients were with unstable BP with statistical significance (Chi-square - 205.2, P - value - <0.001) (Table 4).

Table 4: Distribution of Predictive Markers and Outcome of Septic Patients Before and After Administration of Noradrenaline

Variables	Categories	Before Administration of Noradrenaline infusion	After Administration of Noradrenaline infusion	Chi-square	P value
Predictive Markers	Deranged LFT's	144 (92.3)	34 (21.8)	158.3	<0.001*
	Deranged RFT's	135 (86.5)	38 (24.4)	122.1	<0.001*
	Altered mentation (GCS<15)	156 (100)	14 (9.0)	257	<0.001*
	q SOFA Score>2 (Sepsis)	156 (100)	23 (14.7)	228.3	<0.001*
Outcome	BP-Unstable	156 (100)	31 (19.9)	205.2	<0.001*

**Discussion**

Noradrenaline infusion is supported in bringing the stability of blood pressure (raising the low blood pressure) in septic patients. Dalla, K et al <sup>45</sup> studies reported higher males than females, and our present study is compatible with Dalla, K et al study being males were higher than females in the study.

Jouffroy, R et al <sup>46</sup> study shows a median age of 69 years of patients in their study conducted in reducing the 30-day mortality rate in septic shock patients, we found above 95% of our study patients were <60 years, and only 3.8% of study patients were >60 years of age groups. Baid, H et al <sup>47</sup> in their study concluded, that patients after septic shock treatment, need to quit or reduce their smoking, and alcohol, the personal history of our study subject showed around 30% of each of our patients chewed tobacco, consumed alcohol, and smoked before the treatment.

Bima, P et al <sup>48</sup> reported all their study patients with septic shock showed fever, in our present study, we reported 48.1% of patients became afebrile after infusion of noradrenaline (Chi-square - 83.23, P-value - <0.001). Albertson, T. E et al <sup>49</sup> described their study of patients voided red, yellow, and green coloured urine, and in our study, 13% of patient's urine was into normalization after noradrenaline infusion (Chi-square - 10.68, P-value - <0.001).

Ravikumar, N et al <sup>50</sup> half of the study patients suffered from odema, and our present study reported 9% of patients' odema was recovered after infusion of Noradrenaline (Chi-square - 3.586, P-value - <0.029). Maizel, J et al <sup>51</sup>-study reported low urinary output in 9 patients, we found in this present, 20% of patient's lesser urine output was normal (Chi-square - 13.67, P-value - < 0. 00 1).

Chae, B et al <sup>52</sup> described that altered sensorium was more common in their study patients, in our study, and 21% of altered sensorium was recovered after infusion of noradrenaline (Chi-square - 83. 23, P-value - <0.001). Law, A. C et al <sup>53</sup> reported in their study conducted in both live and deceased patients in whom phenylephrine was infused, and they found phenylephrine lowered the heart rate at one hour by 4 beats/minute, and we found 58.4% of patient's heart rate was normalized after infusion of noradrenaline (Chi-square – 107.2, P-value - <0.001).

Innocenti, F et al <sup>54</sup> studies showed that systolic BP was 73mm Hg before infusion of noradrenaline, and SBP raised to 106 after infusion, in our present study, we found 89.7% of our study patient's SBP was normalized after infusion of noradrenaline (Chi-square – 250.3, P-value - <0.001).

Messina, A et al <sup>55</sup> reported in their study conducted on 127 patients infused with norepinephrine that the patients

showed 15–22 breaths/minute, and patients in the intensive care unit showed 16–25 breaths/minute. We reported 17.3% recovered with a normal respiratory rate after infusion of noradrenaline (Chi-square - 29.96, P-value - <0.001).

Uncu Ulu, B et al <sup>56</sup> described that in their study patient suffered from coldness, cyanosis, and also severe paleness, but after cytokine hemo-adsorption, the patient recovered and amputation was prevented. Our 49.4% and 32.1% of study patients suffered from pallor and cyanosis respectively, but after noradrenaline infusion, 25% and 23.1% of our patients recovered from pallor, and cyanosis is respectively (Chi-square – 20.95, P-value - <0.001), (Chi-square – 25.48, P-value - <0.001).

Huang, J et al <sup>57</sup> reported that in their study using methylene blue as vasopressin improved hemodynamic stabilization including icterus with improvement in jaundice, in our study, we found 48.1% of septic patients were icterus before noradrenaline infusion, and 30.2% were recovered from icterus after noradrenaline infusion (Chi-square – 32.02, P-value - <0.001).

Prakash, S. Y et al <sup>58</sup> studies also reported on patient's recovering from clubbing in post-resuscitation, we also reported 28.95 of patients recovered from clubbing after noradrenaline infusion (Chi-square – 33.77, P-value - <0.001). Feng, F et al <sup>59</sup> study's ROC curve showed that odema was recovered after norepinephrine infusion, our 49.4% also recovered from odema after noradrenaline administration (Chi-square – 27.13, P-value - <0.001).

Alshahrani, M. S et al <sup>60</sup> study shows that after norepinephrine infusion, the odd's ratio showed increased hemoglobin levels in patients, and our study is compatible with Alshahrani, M. S et al study in 38.5% of patients showed improvement in increased hemoglobin level after noradrenaline infusion (Chi-square - 46.222, P-value - <0.001).

Kang, D et al <sup>61</sup> described that in their study along with CD4, and CD8, WBC count also increased after infusion of creatine phosphate, and norepinephrine. 53.2% of our study patients showed improvement in normalization of TLC after infusion of noradrenaline (Chi-square - 91.05, P-value - <0.001).

Stahl, K et al <sup>62</sup>-study author explained that after infusion of norepinephrine, the changes in the septic endothelium led to an increase of platelets in septic patients, we also found an increase of platelets after infusion of noradrenaline in 38.5% of septic patients (Chi-square - 49.76, P-value - <0.001). Zhang, L et al <sup>63</sup> studies found that terlipressin along with norepinephrine yielded improved results in liver perfusion along with improvement in total bilirubin in septic patients, likewise, our study also found improvement of total bilirubin in 28.2% of our septic patients after noradrenaline infusion (Chi-square - 29.13, P-value - <0.001).

Tian, C et al <sup>64</sup>, and Li, C <sup>65</sup> reported the efficacy of norepinephrine infusion, and appropriate antibiotics recovered the septic patient along with normalization of aspartate transaminase, and alanine transaminase, we also found 46.8% and 30.1% of septic patient's aspartate transaminase, alanine transaminase was normalized respectively after noradrenaline infusion (Chi-square – 69.84, P-value - <0.001), Chi-square - 35.21, P-value - <0.001).

Ahmed, R. M et al <sup>66</sup> described that along with arterial pressure, total protein also gained normalization after infusion of norepinephrine, and our study is compatible with them by normalizing 31.4% of septic patient's total protein after noradrenaline infusion (Chi-square - 37.25, P-value - <0.001).

Schneider, F et al <sup>67</sup> disclosed that albumin levels were highly improved after norepinephrine, and our study found 36.5% of our septic patients improved in albumin after noradrenaline infusion. Meyer, E. J et al <sup>68</sup> outlined

that globulin level predicts the mortality rate in septic patients, and after norepinephrine infusion survival rate increased in their patients, we also found similar results of 16/30 have become conventional globulin level after noradrenaline infusion (Chi-square - 4.998, P-value - <0.025).

Dimski, T et al <sup>69</sup> transcribed that urea and creatinine were normalized after norepinephrine infusion, our present study delineated that 73% of patient's urea became normal (Chi-square - 166.6, P-value - <0.001), and 28.2% of patient's creatinine became normal (Chi-square - 28.8, P-value - <0.001) after noradrenaline infusion.

Urban, J. A et al <sup>70</sup> published data explained that septic shock patients due to diabetic infection showed stability of sodium level after norepinephrine treatment, our 23.1% of our study patient's sodium level was normalized after noradrenaline infusion (Chi-square - 25.48, P-value - <0.001).

Lankadeva, Y. R et al <sup>71</sup> experimental study found that potassium was not normalized after infusion of sodium ascorbate, but in our study, we found 9 out of 23 patient's potassium was normalized after infusion noradrenaline (Chi-square - 6.825, P-value - <0.009). Abnormal Potassium (adults <3.5 to >5.2 (mEq/L), children ages 1 to 18 years-<3.4 to >4.7 (mEq/L) was present in 23 (14.7%) patients before administration of noradrenaline and after administration of noradrenaline, only 9 (5.8%) patients were with potassium with statistical significance (Chi-square - 6.825, P-value - <0.009).

Amanullah, A et al <sup>72</sup> published research shows deranged LFTs were improved after noradrenaline infusion, our study was compatible with their study in deranged LFTs, (Chi-square - 158.3, P-value - <0.001), and deranged RFTs (Chi-square - 122.1, P-value - <0.001). In septic patients, there are few predictive markers such as GCS, and author Elbouhy, M. A <sup>73</sup> and team reported that after

noradrenaline infusion, altered mentation was improved with the GC scale. In our present study also we have analyzed and found GC scale improved after infusion of noradrenaline in 91% of our septic patients (Chi-square - 257, P-value - <0.001).

One of the best predictive markers in septic patient's health improvement is quick Sequential Organ Failure Assessment (qSOFA), which was reported improved by several authors Guaracino, F et al <sup>74</sup>, Sahoo, P et al <sup>75</sup>, Singh, K et al <sup>76</sup> in septic patients after noradrenaline infusion. Our present study also reported in 85.3% of patients showed improved qSOFA (Chi-square - 228.3, P-value - <0.001).

As septic patients require noradrenaline infusion for stabilization of blood pressure, 80.1% of our study patients were stabilized after noradrenaline infusion (Chi-square - 205.2, P-value - <0.001), and our study was compatible with Selby, A. R et al <sup>77</sup>-study achieving arterial pressure.

In conclusion, in septic patients, infusion of noradrenaline is like the "magic potion", where every biological marker shows improvement and stabilization earlier than early diagnosis, clinicians especially emergency Medicine physicians require separate alertness in noradrenaline dosage adjustment, the procedure of infusion, observation of improving symptoms, and recording all minor observation also to reduce the mortality occurring due to septic shock.

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