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Original Article

A study of myoglobin changes and its effect on sepsis severity and outcome

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Abstract

Introduction: Sepsis refers to a set of systemic inflammatory responses to infection that cause harmful effects on the human body. Myoglobin can be used as a valuable marker in determining the status of patients with sepsis. This study aims to investigate the changes in myoglobin and its effect on the severity and outcome of sepsis in a hospital setting.

Methods: In this study, patients were divided into three groups: Sepsis, severe sepsis, and septic shock. Relevant data regarding their age, gender, myoglobin level in 4 different times (admission time, 6, 12 and 24 hours later), and Sequential Organ Failure Assessment (SOFA) index were obtained and analyzed. Blood culture was taken for all patients, and the results were evaluated for gram-positive or gram-negative bacteria.

Results: The patients of the three groups were not significantly different in terms of age ($P=0.59$) and heart rate ($P=0.18$), while in terms of myoglobin, there was a significant difference in all studied timeframes ($P=0.00$), length of hospital stay ($P=0.01$), fever ($P=0.00$), and SOFA ($P=0.00$), so that with increasing sepsis severity, these variables were also increased. There is no significant difference in the gender distribution ratio between groups ($P>0.05$). The highest rate of involvement in each group of patients is related to the respiratory tract. The patients' outcome (survival/death) was significantly different among the studied groups ($P=0.00$). A higher percentage of the blood cultures was gram-negative, and the frequency of cultures was not significantly different between the studied groups. ($P=0.86$).

Conclusion: The level of myoglobin measured in patients had an increasing trend. Elevated myoglobin levels were also significantly associated with sepsis and mortality.

Introduction

Myoglobin is a heterodimer compound, composed of a peptide chain and a heme group. The molecular weight of myoglobin is approximately 17.9 kDa. This protein is found in skeletal and heart muscles in the human body. When, for any reason, these tissues are damaged, the myoglobin in the cytoplasm of these cells is quickly released and enters the bloodstream. This is why myoglobin is used as a marker to determine heart and skeletal muscles damage.[1]

Sepsis refers to a systemic inflammatory response to an infection that causes harmful effects on the human body. This systemic inflammatory response has several stages, including sepsis, severe sepsis, and septic shock. Despite the differences in the severity of symptoms, all of them are life-threatening.[2]

According to the definition provided by the American Society of Thoracic Physiologists, there must be at least two of the following criteria present in a patient to be referred to as septic disease[3]: 1. Body temperature over 38°C or less than 36°C, 2. Tachycardia over 100 beats per minute, 3. Tachypnea over 20 breaths per minute, or P_{CO2} < 32, and 4. White blood cell (WBC) counts > 12000, or band cells more than 10%. Whenever there is one of the following criteria in the disease in addition to the above, it is classified as severe sepsis[4]: 1. A lowered level of consciousness, 2. Pa_{O_2} < 75, 3. Oliguria less than 0.5 cc/kg for more than two consecutive hours, 4. Liver dysfunction or bilirubin more than 43 mmol/dL, 5. Metabolic acidosis with base excess (BE) > 5, and 6. prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) 1.2 times greater than the upper limits of normal, platelet count less than 75,000, or a drop in platelet levels to half within 24 hours.

Septic shock is a condition of severe sepsis in which, in addition to the above, the hypotension requires supportive treatment and the average capillary pressure remains below 70 mm Hg for more than 30 minutes, despite adequate fluid therapy.[5] Based on the above, it seems that myoglobin can be used as a beneficial marker in determining the status of patients with sepsis. This study aimed to investigate the changes in myoglobin level among the septic patients and its effect on the severity and

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outcome of sepsis to use logical correlation in practice as a prognostic and diagnostic factor.

Methods

The present cross-sectional study was conducted from the first of October 2016 to the end of March 2016. During this study, all patients who complied with the international definition of sepsis criteria and were defined as septic entered the study after obtaining informed consent. The checklist containing blood myoglobin levels, conflict zones, sex, age, and survival rate was filled, and the data was collected. The sample size was determined using the two-ratio comparison formula in the intervention studies, considering the maximum error of the first type as 0.05, and the study power as 80% based on the study of Yao et al., in which the higher levels of myoglobin were associated with higher mortality among the septic patients.[5] in this study, to determine the association of myoglobin with death in patients with sepsis, 25 samples were needed in each of the three groups. By considering a 10% drop up, a total of 90 samples were determined in 3 equal groups.

In the present study, first patients who met the criteria for admission and were compatible with the definition of sepsis entered the study. Based on the sepsis severity and definition, patients were divided into three categories: Sepsis, severe sepsis, and septic shock. Finally, the patients were compared and examined after being placed in these three groups. Patients were also examined for age and sex. Blood culture was obtained from all the enrolled patients, and the results were evaluated for the presence of gram-positive or gram-negative bacteria. In septic patients, the infection site was determined, and the patients were classified based on it (In 5 categories: respiratory tract infection, urinary tract infection, brain infection, gastrointestinal infection, and infection of unknown origin (e.g., osteomyelitis, endocarditis, etc.). Patients entered the study less than 48 hours after the onset of symptoms to prevent the effect of sepsis duration on the results. Patients with the following criteria were excluded from the study:

1. Patients who have had a recent myocardial infarction, 2. Patients who have recently had acute pancreatitis, regardless of the etiology, 3. Patients with sepsis of soft tissue origin, 4. Patients with recent rhabdomyolysis, 5. Patients who have ischemia, regardless of the etiology, 6. The patients with limb ischemia, regardless of the etiology, including diabetes, 7. Patients with a history of coronary heart disease, 8. Patients with a history of any malignancy, 9. Pregnancy, 10. Autoimmune and vascular collagen diseases, 11. Patients with a history of recent hospitalization, and 12. Patients with immunodeficiency (splenectomy, immunosuppression, etc.).

In this study, a checklist was prepared for each patient, and the obtained information was recorded using this checklist. One of the variables studied in this study was the patients' length of hospital stay. Patients were also monitored after discharge, and their survival was assessed for 28 days after hospitalization. For all the patients in the study, myoglobin levels were checked four times. First, the level of myoglobin was checked for all patients at the time of referral. Then at 6, 12, and 24 hours after the visit, the blood myoglobin levels were rechecked among all the groups to evaluate the increasing or decreasing course.

From the time of referral for research samples, the vital signs were charted, and the fever, blood pressure, and heart rate at the beginning of the visit were evaluated and compared. WBC and platelet counts were also evaluated among the three groups. Also, during this study, the Sequential Organ Failure Assessment (SOFA) index was calculated for the studied patients, and the difference of this index was studied among them.

Statistical analysis was performed using SPSS 16.0 software. The data obtained from the study were analyzed using descriptive statistical methods (Mean ±standard deviation, frequency, and percentage), one-way variance analysis test and chi-square relationship test, or Fisher exact test, and statistical analysis. In this study, a *P* value of less than or equal to 0.05 was statistically significant

Results

The study included 90 people, who were divided into the three following groups based on the severity of the disease: Sepsis, severe sepsis, and septic shock. There were 30 people in each group. The mean age of the patients was 55.9 ± 11.9 years. The youngest patient was 28 years old, and the oldest one was 90 years old. Among the participants, 46 were men, and 44 were women.

As is seen in Table 1, the mean age of the patients, as well as the mean heart rate, did not differ significantly between the groups. Other measured variables differ significantly between patients in different groups. Sepsis group included 14 men and 16 women, the severe sepsis group included 15 men and 15 women, and the septic shock group included 17 men and 13 women. There is no significant difference in gender distribution between the groups ($P > 0.05$).

As shown in Figure 1, the highest rate of involvement in each group of patients is related to the respiratory tract, which is higher among septic shock patients compared with the others. Comparing the high percentage of each conflict zone between different groups showed no significant difference between them (*P* value = 0.92).

As shown in Figure 2, the highest discharge rate was reported in the sepsis group and the highest rate of deaths in the septic shock group. The proportions of the consequences occurring in different groups differ significantly (*P* value = 0.00).

According to Figure 3, similarly, in all groups, a higher percentage of the blood culture results was gram-negative. The comparison of the groups showed that the frequency ratio of the culture results did not differ significantly between different groups (*P* value = 0.86).

Table 1. Comparing patients' characteristics in different groups

		Lowest	Highest	Mean	*P* value
Age	Sepsis	30	86	56.73	0.59
	Severe sepsis	28	90	56.83	
	Septic shock	32	84	54.06	
Myoglobin 0	Sepsis	125	486	226.74	0.00
	Severe sepsis	162	345	268.26	
	Septic shock	241	411	331.42	
Myoglobin 6	Sepsis	218	978	423.96	0.00
	Severe sepsis	396	741	553.26	
	Septic shock	324	912	678.93	
Myoglobin 12	Sepsis	485	948	703.9	0.00
	Severe sepsis	578	1002	810.33	
	Septic shock	796	1124	1019.63	
Myoglobin 24	Sepsis	528	1249	854.46	0.00
	Severe sepsis	762	1480	1115.56	
	Septic shock	1042	1800	1372.73	
Length of stay	Sepsis	4	7	87.4	0.00
	Severe sepsis	5	18	8.7	
	Septic shock	4	23	10.26	
Body temperature	Sepsis	37	40.7	38.81	0.019
	Severe sepsis	37.5	40.80	38.99	
	Septic shock	37	40	39.57	
Heart rate	Sepsis	54	140	99.96	0.18
	Severe sepsis	59	148	102.63	
	Septic shock	59	148	111.2	
DBP	Sepsis	45	115	85.33	0.001
	Severe sepsis	40	115	81.33	
	Septic shock	45	105	68.8	
SBP	Sepsis	66	190	156.66	0.00
	Severe sepsis	80	190	147.5	
	Septic shock	75	180	120.5	
SOFA	Sepsis	4	9	6.96	0.00
	Severe sepsis	5	11	8.06	
	Septic shock	7	13	10	

DBP, Diastolic blood pressure. SBP: Systolic blood pressure. SOFA: Sequential organ failure assessment.

Evaluating myoglobin levels in 4 measured periods showed that myoglobin levels increased in all groups over time. Frequent measurement test results showed that this increase was significant in all three groups over time (*P* value = 0.00).

Considering the correlation coefficients, it can be said that in all groups, myoglobin level has a positive and significant relationship with hospitalization days, body temperature (BT), and SOFA score, while the relationship between this variable and systolic blood pressure (SBP) and diastolic blood pressure (DBP) is negative and significant. In other words, with increasing myoglobin levels, we see a significant increase in the number of hospital days, BT, and SOFA, and a significant decrease in SBP and DBP. According to the results, no significant relationship was observed between myoglobin levels and heart rate in any group (Table 2).

Discussion

This study aimed to investigate the myoglobin changes and their effect on sepsis severity and outcome. There were 90 participants in the study, who were divided into three groups based on the severity of the disease: Sepsis, severe sepsis, and septic shock, each group consisted of 30 patients. The mean age of the total patients was 55.9 ± 11.9 years, but there was no significant age difference between the different groups.

The participants' gender composition included 46 males and 44 females, with no significant difference in the sex distribution ratio between the groups, indicating that gender was not a factor in the disease's incidence or severity.

Myoglobin has long been used extensively in the diagnosis of heart damage.[3] Several recent studies have shown that in patients with malignancy, the level of myoglobin in the blood increases significantly with the

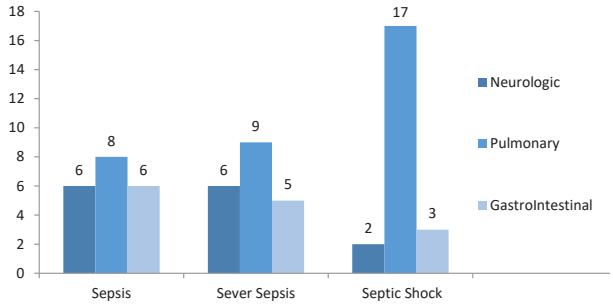

Figure 1. Comparison of conflict in three groups of patients

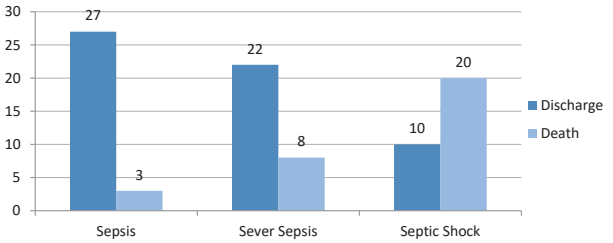

Figure 2. Comparison of disease outcome in three group of patients

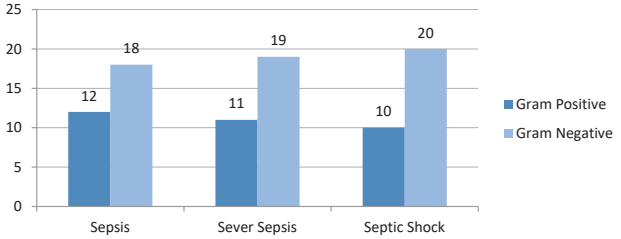

Figure 3. Comparison of culture results in three group of patients

Table 2. Correlation between myoglobin and variables in each group

		Length of hospital stay	BT	PR	DBP	SBP	SOFA
Sepsis Group Myoglobin	Correlation coefficient	0.43	0.21	0.085	-0.34	-0.34	0.511
	P	0.00	0.03	0.42	0.01	0.01	0.00
Severe Sepsis Group Myoglobin	Correlation coefficient	0.48	0.317	0.179	-0.372	-0.426	0.564
	P	0.00	0.00	0.09	0.00	0.00	0.00
Septic Shock Group Myoglobin	Correlation coefficient	0.57	0.31	0.17	-0.36	-0.44	0.52
	P	0.00	0.00	0.1	0.00	0.00	0.00

BT, Body temperature; DBP, Diastolic blood pressure; SBP, Systolic blood pressure; PR, Pulse rate; SOFA, Sequential organ failure assessment.

diagnosis of sepsis, shock, trauma, and burn. Thus, it has been suggested that myoglobin levels may reflect the severity of the disease and the patients' malaise.[4] In our study, the level of myoglobin measured at every timeframe was significantly different between the three groups. The highest rates were in the group of patients with septic shock, severe sepsis, and sepsis, respectively. Therefore, it can be considered that the level of myoglobin can indicate and predict the severity of sepsis.

Our study also showed that myoglobin levels could be used as a diagnostic factor in the early hours of hospitalization. Surveys of patients showed that the highest number of discharges was reported in the sepsis group, and the highest number of deaths was reported in the septic shock group. Also, the results of the study by Liu et al showed that serum levels of myoglobin and APACHE-II index in the survival group were significantly lower than the death group. Also, with increasing serum levels of myoglobin, mortality increased in patients with sepsis, and there was a positive and significant correlation between serum myoglobin levels and APACHE-II score.[6]

Therefore, it can be said that determining the serum level of myoglobin can indicate the severity of the disease and the prognosis of patients with sepsis. A study by Martin et al also showed that high levels of myoglobin were positively and significantly associated with mortality in septic patients.[7]

Other studied variables, such as hospitalization days, fever, DBP, SBP, and SOFA were significantly different between different groups, so that the number of hospitalization days, fever, and SOFA were higher in septic shock patients and the sepsis, and the group was lower than the other groups. However, the SBP and DBP were higher in the sepsis patient group comparing with the other groups. The results of a study by Galluzzo et al showed that in all studied groups, myoglobin levels had a positive and significant relationship with hospitalization days, BT, and SOFA score, while the relationship between this variable and the SBP and DBP was negative and significant. [3] In other words, with increasing myoglobin levels, we see a significant increase in the number of hospital days, BT, and SOFA, and a significant decrease in systolic and diastolic blood pressure.

Mortality due to severe sepsis has also increased significantly.[8] The highest rate of involvement in each group of patients is related to the respiratory system, which is higher among septic shock patients than others. Also, a higher percentage of blood culture results were gram-negative. The group comparisons showed that the frequency ratio of the blood cultures results did not differ significantly between groups. The results of a study by Esteban et al. also showed that more than 50% of the results of cultures were gram-negative.[9]

In all groups, myoglobin levels increase over time. Frequent measurement test results showed that this increase was significant in all three groups over time. In a study by Yao et al, who examined the correlation between serum myoglobin levels and septic severity in patients in three groups of sepsis, severe sepsis, and septic shock, the results showed that myoglobin levels gradually increase within 24 hours after admission.[5] A study by Ye et al also showed that the severity of the disease, APACHE II score and the mortality rate increased with the increase of myoglobin levels. The results also showed that myoglobin level and APACHE II score were the most important parameters for predicting survival rate, where myoglobin level had a higher score.[10]

Conclusion

The levels of myoglobin measured at all times were significantly different between the three groups. As the severity of the disease increased, myoglobin levels increased, and high myoglobin levels were positively and significantly associated with septic patients' mortality. Therefore, it can be concluded that myoglobin level can indicate and predict the severity of sepsis. According to the results of this study, in future research, it is recommended to investigate the relationship between myoglobin level and disease severity in trauma cases, myoglobin level and severity of burn patients, mortality rate, and survival of patients with high myoglobin levels. Factors such as gender, age, and type of disease should also be considered.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Ethical Approval

The ethical approval which was attained from the local medical ethics committee of Tabriz University of Medical Sciences is 95/3-13/4. Additionally, informed consent was obtained from all

Study Highlights

What is current knowledge?

- Myoglobin can be used as a beneficial marker in determining the status of patients with sepsis.

What is new here?

- The level of myoglobin measured in patients had an increasing trend. Elevated myoglobin levels were also significantly associated with sepsis and mortality.

individuals who participated in this study.

Authors' Contribution

AG and HM designed the research. VH gather the data and summarized it. AG and VH performed the statistical analysis and RRG reviewed the quality of the manuscript and revised it and all the authors read and approved the manuscript.

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