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The effect of selenase on the disease process of patients with septic shock admitted to the intensive care unit: A clinical trial in Tehran

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ABSTRACT

Purpose: Despite discovering new antibiotics, mortality due to septic shock has remained high. This research has examined the effect of selenase in patients with septic shock admitted to the intensive care unit (ICU) of a hospital in Tehran.

Materials and Methods: This double-blind clinical trial was done on 80 participants (40 case and 40 control) who were admitted to the ICU with septic shock. Every participant in the case group was administered 500 µg selenase twice daily for 10 days. In contrast, each participant of the control group was treated with placebo (normal saline). Data were collected by observation and recorded in a questionnaire. Chi-square and Student's *t*-test were used for data analysis.

Results: In this study 34 participants (42.5%) were men and 46 (57.5%) were women. The duration stay in the ICU in treatment group was less than in the observation group which was statistically significant ($P = .01$). There was also a significant difference regarding the frequency of morbidity and mortality rates between the two groups ($P = .03$ and $P = .02$, respectively).

Conclusion: Selenium at a dosage of 500 µg (twice daily) is effective in those who have suffered from septic shock. Still, more studies are needed to determine the best dosage and administration method of this drug.

Keywords: selenase; septic shock; intensive care unit; Tehran; disease process.

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INTRODUCTION

Sepsis or blood infection is a condition where the body is fighting a severe infection. It is the body's systemic response to pathogens that might cause infection, fever, tachycardia, and leukocytosis. In other words, sepsis is a spectrum of diseases that includes local inflammation and severe generalized inflammatory response and multiple organ failure.[1,2]

Different stages of sepsis start from a bacterial infection of the blood (bacteremia). If this infection is left untreated, it leads to sepsis and severe sepsis. In its advanced stages septic shock occurs which has more mortality than the milder stages, i.e.in 50-80% of cases.[2-4]

Most common organisms in sepsis are: streptococcus pyogenes, streptococcus pneumoniae, staphylococcus aureus and neisseria meningitides. Through bacterial components such as endotoxin and lipoteichoic acid and its effect on neutrophils and macrophages, a wide range of pro-inflammatory factors, including IL1, IL6, TNF-α, the host confronting regulatory responses, IL4, IL10, are instilled. They also stop production of pro-inflammatory cytokines.[5-10] Selenium is an essential mineral with an important functional role in immunity, health and body function. It has also had an enzyme role

in many clinical trials used to treat the patients. Selenium is prescribed in the hope that it can balance the low selenium concentrations in patients who have suffered from septic shock and to provide pharmacological impact via antioxidant defense.[5,11]

Zimmerman and colleagues conducted the first study on the effect of selenium on mortality rates of 40 patients in 1997. They reported no significant effect for it in those who had severe systemic inflammatory response syndrome, sepsis, or septic shock.[13] There have been controversies on the effect of selenium and some of studies have found it effective on the treatment of patients with septic shock and other diseases.[12-15]

Despite discovering new antibiotics, mortality due to septic shock has remained high. Effective treatment of disease and underlying factors in sepsis is important for the treatment of septic shock. Prevention is still the best cure.[2] Preventive measures include: reducing the number of invasive procedures, limiting the use of fixed-term vascular and bladder catheters, reducing the incidence and duration of severe neutropenia, aggressive treatment of localized infections, and immunization of patients against specific pathogens.[16-18]

Reducing mortality in the intensive care unit (ICU) is still a major challenge.[19,20] Unfortunately, in patients who have suffered from his situation, the use of common medications and treatment techniques such as corticosteroids,[16,17,21,22] immunoglobulins,[16,23-27] bicarbonates[28,29] and arginine[30-34] are not effective and have no considerable impact. Therefore, it seems that due to the antioxidant properties of selenium and its other features, it can maintain and stabilize the vascular endothelium and normal body perfusion. So using selenium compounds for treatment is more appropriate and impressive.

This clinical trial has examined the effect of selenase in patients with septic shock admitted to the ICU of a hospital in Tehran.

MATERIALS AND METHODS

This randomized, double-blind clinical trial was conducted on the patients admitted to the ICU of Imam Reza Hospital in Tehran with septic shock. Pilot study was done on a sample of 10 specimens, based on the mean arterial pressure in mm Hg. So the required sample size was 80 participants (40 patients in the placebo group and 40 patients in the treatment group). The specimens were sampled using simple random sampling. Method of allocating participants into two groups was based on the simple random sampling using the black and white cards. Confidence level was 95%.

All participants were in age range of 20 to 90 years old suffering from septic shock, positive bacterial culture, Peoria, positive radiographic abscess, pneumonia, cellulites, gangrene and infection in the presence of a urinary catheter since being admitted to the ICU. Informed consent was taken and if the patient was not conscious, signed consent was taken from his/her first degree relatives. The patients who had chronic liver disease and active gastrointestinal bleeding or were on dialysis, pregnant and post cardio-pulmonary resuscitation were excluded from the trial.

The study protocol was approved by ethics committee of AJA University of Medical Sciences. Data were collected by observation and recorded in a questionnaire. Anthropometric data such as age and gender were gathered and the amount of each studied variable in both groups were also recorded before starting the treatment. Every participant in the treatment group was administered 500 µg selenase twice daily for 10 days. In contrast, each participant of the observation group was treated twice daily for a period of 10 days with placebo (normal saline). At the end of treatment, the studied variables were recorded again.

Chi-square test was used to assess the status of two groups in respect of variables such as age, gender and frequency of morbidity and mortality rates. Student's *t*-test was used to evaluate the mean level changes of plasma variables in the two groups. The Statistical Package for Social Sciences (SPSS) software version 18 was used for statistical analysis. *P values* less than.05 were considered significant.

RESULTS

In this study 34 (42.5%) participants were men and 46 (57.5%) were women. No significant differences were found between demographic data (age, sex and weight) **(Table 1).** The mean age of patients was 58.25 ± 17.6 years old in the treatment group and 59.25 ± 16.4 years old in the observation group, repectively. The age ranges were 22 to 85 years old in the control group and 24 to 90 years old in the observation group, repectively. There was no significant difference between the groups in this regard ($P = .01$).

Frequency of the variables and individual characteristics such as the source of infection, pathogenicity factors and co-morbidities are listed in **Table 3**. There was no significant difference between the patients individual characteristics in the two groups ($P = .22$). The prevalence of diabetes was higher than all other co-morbidity diseases.

Table 1. The demographic characteristics of patients in the two studied groups

Variables	The frequency of individuals in groups according to age group		*P* Value
Age Groups	Observation group	Control group	
20-30	2	3	.08
31-40	2	3	
41-50	2	6	
51-60	12	10	
61-70	8	7	
71-80	5	6	
81-90	7	5	
Sex ratio (female to male)	17 to 23	19 to 21	

Table 2. Comparing mortality, morbidity and duration stay in ICU in two studied groups

Variable	Case Group	Control Group	*P* Value
Mortality	6	9	.023
Length of ICU (day)	13	18	.018
Morbidity	3	6	.035
Acute respiratory distress syndrome	2	1	.029
Chronic renal failure	1	2	.041
Pulmonary embolism	0	3	.036

The duration stay in the ICU in treatment group was less than in the observation group which was statistically significant (P =.01). There were also significant difference regarding the frequency of morbidity and mortality rates in participants with septic shock between the two groups (P =.03 and P =.02, respectively). Six patients (15%) in treatment group and nine patients (22.5 %) in the observation group died **(Table 2)**.

There was a significant difference between the rate of Pao2/Fio2 lower than 200 in the two groups (P =.01). Thus, 21 patients (52.5%) in the treatment group and 25 patients (62.5%) in the observation group had Pao2/Fio2 lower than 200 **(Figure 1)**.

Other laboratory findings such as markers of the acute phase response were examined in this study include increased platelet count and CRP (C-Reactive Protein). platelet count and C-Reactive Protein in the two groups were statistically significant. Five patients in the treatment group and nine patients in the observation group had a platelet count below 150, 000 dL. This decrease

Table 3. Comparing the two studied groups in case of site of infection, pathogen and comorbidity

Variable	Case Group	Control Group	*P* Value
Site of infection			> .05
Pneumonia	9	8	
Osteomyelitis	5	3	
Meningitis	1	2	
Peritonitis	9	6	
Gluteal abscess	3	3	
Narcotics injecting (Bacteremia)	7	9	
Urinary tract infection	9	9	
Pathogen			> .05
Anaerobic	10	12	
Fungi (Candida and Aspergillus)	7	9	
Gram positive	10	8	
Gram negative	13	11	
Comorbidities			> .05
Diabetes mellitus type1	6	5	
Diabetes mellitus type2	7	8	
Cerebrovascular accident	4	5	
Ischaemic heart disease	5	6	
Chronic obstetric pulmonary disease	9	10	
Hypertension	9	6	

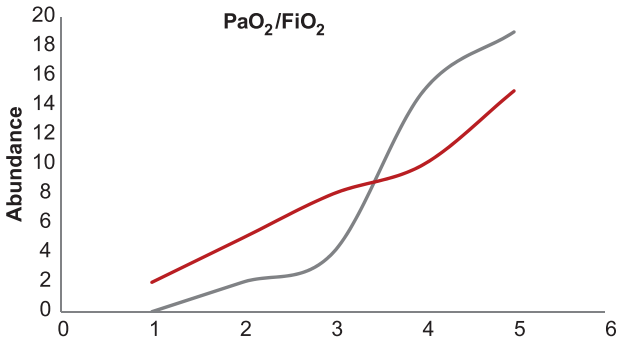

Figure 1. Comparing PaO_2/FiO_2 in the two studied groups.

in platelet count was 70000-120000 among the patients. Increased levels of cardio-pulmonary resuscitation in test results were observed in 13 patients of the placebo group and eight patients of the control group **(Figure 2, 3)**.

DISCUSSION

Based on the findings of this study, no significant association was found between the study variables and demographic data of the studied groups. There was a direct association between the incidence of infection and duration of stay in ICU. Duration of stay in ICU for treatment group was less than the observation group. ICU stay duration after being in operation is an expensive part of any hospital's management.

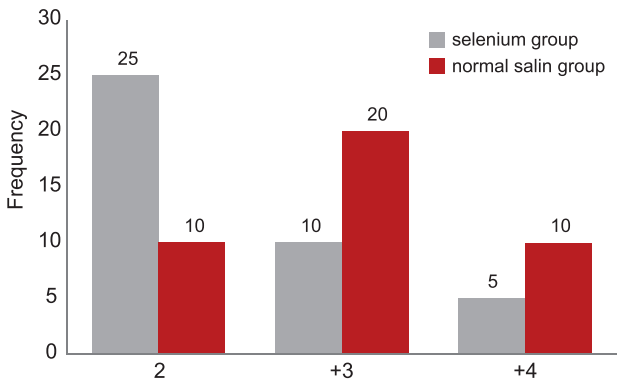

Figure 2. Comparing C-Reactive Protein in the two studied groups.

In a clinical trial on 20 patients with severe burns, Berger and colleagues concluded that selenium supplementation significantly reduces infection bronchopneumonia and the duration of ICU stay.[35] Their results are consistent with the results of our study. In a meta-analysis of nine randomized clinical trials to evaluate the effect of selenase on 792 patients, the results showed that selenium was effective in reducing mortality and duration of stay in patients in ICU. However, selenase had no effect on pneumonia.[15] Similar to our findings, in another study on 18 trauma patients with bullet wounds, a significant association was found between less duration of ICU stay and using selenium supplements.[36]

Sepsis is a common cause of death in the ICU and the 13 th leading cause of death in United States.[37] Many factors contribute to the risk of mortality due to sepsis including an underlying medical condition, age and multiple organ failure.[38-40] A large cohort study in the United States showed that sepsis and septic shock occur in 28% of hospitals.[39] Also, a multicenter study in Europe showed that ICU mortality was 27% and overall hospital mortality rate was 36%.[40]

In this study, no significant association was observed between the control group mortality rate (15%) and mortality rate in patients who had received selenium in the observation group (22.5%). Heyland and colleagues

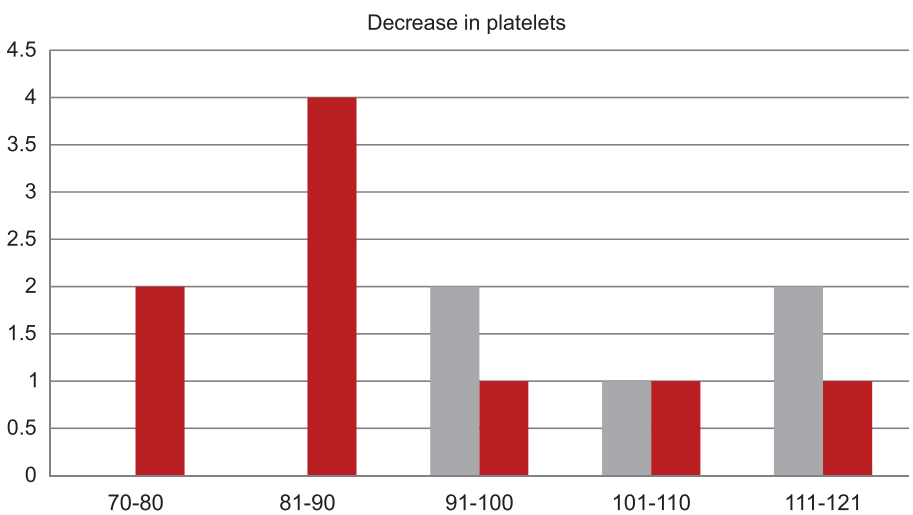

Figure 3. Comparing platlate in the two studied groups.

showed that serum concentrations of selenium reduce the mortality rate.[13] Also, Alhazzani and colleagues showed the efficacy of selenium in reducing mortality of ICU patients.[15] Findings of this study were consistent with the results of our study.

The first clinical trial of the effect of selenium was done in 1997 on 40 patients (20 patients in the control group and 20 patients in the observation group) by Zimmerman and colleagues. They administered selenium bolus to patients and 1000μg of selenium daily for 28 days. They concluded that selenium has no effect on the mortality rate of patients with systemic inflammatory response syndrome.[12] Their results are consistent with the findings of our study. In another study by Avenell and colleagues on 813 patients, there was insufficient evidence to recommend selenium supplements. In this regard, a study had suggested that their research was poor and that was why they did not find sufficient evidence.[41] Another meta-analysis of 21 clinical trials with more than 2400 patients found a significant association between reduced mortality and reduced long-term need for selenium in patients receiving mechanical ventilation.[42]

Early diagnosis of sepsis and using evidence-based treatment as soon as possible is essential to improve treatment outcomes and to reduce the mortality of sepsis.[43,44] Actually, shortening of the diagnosis time of severe sepsis is vital in reducing morbidity and mortality rates of the disease.[45] In our study, no significant difference was observed in mortality between the two studied groups. Saker and colleagues have stated that tissue damage, organ dysfunction, and infection have a significant relationship with low level of plasma selenium.[14] In another study conducted in Germany, the effect of sodium selenite was further elaborated. In their study on 60 patients scheduled for cardiac surgery, Stoppe and colleagues found a relationship between plasma levels of sodium selenite and organ failure. So the patients who had lower plasma levels of selenium were more likely to have organ failure.[46]

A criterion for weaning from mechanical ventilation and acute respiratory distress syndrome is assessing the condition of patients in the Pao_2/Fio_2. In our study, patients Pao2/Fio2 ratio in the control group was higher than the placebo group which was statistically significant. In a study in 2007 on effects of high doses of selenium on 60 patients with septic shock, no significant relationship was found between Pao2/Fio2 of patients in the treatment and control groups.[47] Angstwurm and colleagues also did not find any significant correlation between the under ventilated days and patients Pao2/Fio2 ratio in their studied groups (selenium and placebo).[48] In a survey by Berger and colleagues, the number of ventilator days in the control group (median 5-day period of 12.2 days) and the number of ventilator days in the placebo group (mean 2-day period of 19.1 days), there was no statistical difference between the two groups.[49] In a multicenter study Angstwurm and colleagues' findings were similar to their previous findings which showed no significant association between their two studied groups.[50] Their findings are not consistent with our study.

Jalalian and colleagues have examined the affecting factors in patients weaning from the ventilator. In their study Pao_2 / Fio_2 was identified as an affecting factor. The time of separation from mechanical ventilation in patients who had Pao2 / Fio2 lesser than 200 was 3.91 ± 0.82 days, in the group who had Pao2 / Fio2 between 200 to 300 was 3.87 ± 0.43 days and the group who had Pao2 / Fio2 more than 300 was 3.23 ± 0.29 days. However, this increased Pao2 / Fio2 ratio was affected in the short-term, but its reduction was not statistically significant.[50]

In the present study the acute phase responses of the two groups had significant difference. In 2008 Berger and colleagues studied the impact of rapid administration of antioxidant supplements in the early hours of ICU admission on limb function in patients with severe disease (surgery trauma and subarachnoid hemorrhage). They divided their patients into groups receiving supplemental antioxidants (including vitamins B and C, zinc oxide and selenium) and placebo. They observed that the levels of the inflammatory marker of cardio-pulmonary resuscitation in the group that had received the antioxidant supplements were much lower than the placebo group. Also, cardio-pulmonary resuscitation levels reduced in those who had received antioxidant very rapidly.[49] In a study the level of C-reactive protein was lower in the group who had received selenium.[51] Also, Salma and colleagues have stated that plasma concentrations of selenium inversely correlate with serum levels of C-reactive protein, IL-6 and procalcitonin.[54] The results of these studies are quite similar to the present investigation.

In our study, the prevalence of patients with a platelet count below 150, 000 dl in the control group (selenium) was lower than the placebo group. Some studies have also stated that there is a relationship between thrombocytopenia and patients with unfavorable outcome.[53-55] The results of these studies were consistent with our results.

Forceville and colleagues have examined the effects of high dosages of selenium on patients with septic shock. The results of their study showed that the mean of platelet

in patients who had received selenium was less than the placebo group which was not significant.[49] Some studies have suggested that in men with coronary heart disease, platelet levels are inversely associated with plasma levels of selenium.[56,57] The results of these studies are consistent with the findings of our study.

Using catecholamines to preserve life and tissue perfusion in exposure the life-threatening hypotension is required. It is necessary, even when it is still not solved hypovolemia. So there may be some patients who have a minimum pressure perfusion and maintain enough flow, needing vasopressor therapy. Studies have shown that administration of norepinephrine to maintain mean arterial pressure at least 65 mmHg, protects the tissue perfusion.[58,59] In this study the number of days that patients require administration of catecholamines (norepinephrine) in the control group was less than the placebo group and this difference was statistically significant. In this regard, Forceville and colleagues study 13 patients in the control group (selenium) and 19 patients in the placebo group needed norepinephrine catecholamines. The results of his study indicate the clinical efficacy of selenium in reducing the need for norepinephrine in patients, but this difference was not statistically significant.[47] Forceville results are consistent with the results of our study.

Norepinephrine has many advantages compared to dopamine and other catecholamines. It is the first choice in shock. Norepinephrine is stronger than dopamine and it can be more effective to resolve the hypotension in patients with septic shock. With increase in stroke volume and heart rate, dopamine can increase mean arterial pressure and cardiac output. However, norepinephrine can increase mean arterial pressure with vasoconstriction and small changes in heart rate and lower increased stroke volume.

The findings of six randomized trials for comparing norepinephrine and dopamine do not supported the routine use of dopamine in septic shock management.[60,61] Many studies have expressed lower mortality rate and incidence of adverse events in using norepinephrine instead of dopamine.[62,63] Dopamine is more arrhythmogenic compared to norepinephrine.[64]

Study limitations

Unfortunately, because of the high costs, measurement of serum prolactin levels was not done.

CONCLUSION

Selenium at a dosage of 500µg (twice daily) is effective in those who have suffered from septic shock. Still, more studies are needed to determine the best dosage and administration method of this drug.

Although clinical treatment of patients with septic shock is a dynamic and evolving process, new clinical methods with different approaches to the treatment of sepsis and septic shock have been introduced. Also, international guidelines on the treatment and survival of patients have played a significant role. Still the need to conduct further multicenter clinical trials in this regard and integrating and combining the clinical knowledge and experience to generalize the results of evidence-based clinical studies are required.

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CONFLICT OF INTERESTS

None declared.

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