Progress in Nutrition 2019; Vol. 21, N. 3: 605-610 DOI: 10.23751/pn.v21i3.8672 

Original article

# Is it given over importance to serum zinc level in patients with sepsis?

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**Summary.** *Background:* Sepsis is a systemic inflammatory response to infection, life-threating and one of leading causes of death in intensive care units. The aim of this study is to determine relation between mortality and daily required doses of zinc replacement in adult patients with sepsis. *Subjects and Methods:* This retrospective study was carried out in internal medicine intensive care unit (ICU) of Gaziantep University Hospital. A total of 264 patients patients with sepsis in ICU, who are with low serum zinc level at admission (*n*=132) and not (*n*=132) included in the study. *Results:* 28 and 90-day mortality have been found higher in patients with normal serum zinc level at admisson to ICU than other group as 53.8% and 91.8%, respectively (p<0.001). There was a statistically significant correlation between serum zinc levels, SAPS and SOFA scores, respectively (*r*: -0.232, *p*<0.001 and *r*:-0.260, *p*<0.001). *Conclusion:* The findings show that zinc replacement by daily required dose has no effect on 28 and 90-days mortality in septic patients with low serum zinc levels at the time of admission to ICU. Further prospective, randomized controlled trials to compare of daily required and higher doses of zinc supplementation should carry out.

**Key words:** sepsis, zinc, supplementation, long of stay, mortality

## Introduction

The first definition of sepsis, whose name originated from ancient Greece was made in the early 1600s BC (1). There have been major changes in definition, demographics characteristics and management of sepsis recently. In 1991, sepsis was defined as having at least 2 systemic inflammatory response syndrome criteria along with a definite or possible infection focus (2). Criteria for systemic inflammatory response syndrome are: 1. Temperature >38°C or <36°C ; 2. Heart rate >90 beats per minute; 3. Respiratory rate> 20 breaths per minute or PaCO2< 32 mmHg and 4. White blood cell count >12,000/cu mm, <4,000/cu mm, or >10% immature (band) forms. The most recent definition of sepsis is ≥2 qSOFA as well as a suspected/diagnosed infection. Clinical criteria of qSOFA consists of these parameters: 1. Altered mental status (GCS score <15), 2. Systolic blood pressure < 100 mmHg, 3. Respiratory rate >22/minute (3).

The incidence of sepsis, which is the most important cause of death in intensive care units, has been increasing in recent years (4-7). A recent published article has been found the incidence of sepsis as 427 per 100.000 in the US population (8). In patients with sepsis, proven recommendations are needed due to management difficulties and high mortality. In recent research, it has been found that the cost per case is 12000 $ in patients with sepsis who did not require mechanical ventilation, whereas the cost has been increased to 40000 $ per case in patients with sepsis requiring mechanical ventilation (9). In patients with sepsis, which an acute catabolic process begins, the nutritional requirement increases. As a result, mobility occurs for glucose synthesis in glycogen and adipose tissues, which are energy stores in patients with sepsis.

Therefore, nutrition is very important in patients with sepsis. Although nutritional guidelines focus on calorie requirements in patients with sepsis, there is not detailed recommendation about zinc supplementation.

A proper immune response is required to battle with microorganisms in patients with sepsis. Zinc homeostasis gains importance in effective immune response. Zinc deficiency may develop in patients with sepsis due to increased nutritional requirements. Because zinc is not stored in human body. In patients with zinc deficiency, adequate cytokine synthesis cannot be performed in the liver and may be insufficient to fight with infectious agents (10).

In this study, it has been measured the concentrations of zinc in blood samples of ICU patients and assessed its clinical significance.

## Materials and methods

*Study participants*

Patients with sepsis who were admitted to the intensive care unit of Gaziantep University were selected randomly. A total of 132 patients with sepsis (97 males and 75 females) with normal serum zinc levels and 132 patients with sepsis (80 males, 52 females) with low serum zinc levels when have been accepted to intensive care unit were included to this study, with their written, informed consent. The reference range of serum zinc concentration in the kits for which blood samples was determined between 66-120 ug/dL by the manufacturer. The patients with serum zinc levels less than 66 ug/dL were included to group 1 and the patients with zinc levels between 66-120 ug/dL were included to group 2. The patients with sepsis have been diagnosed according to the European Society of Intensive Care Medicine and the Society of Critical Care Medicine 2016 criteria. In accordance with the ASPEN heavy metal replacement guideline and prospectus of the drug, it is given parenterally to all patients daily preparations containing 5 milligrams of zinc per day after taken blood samples to measure basal serum zinc level (Tracutil®, B.Braun Melsungen AG) (17). The patients were divided into two groups according to serum zinc level as soon as admitted to intensive care unit. Detailed data, age, sex, biochemical parameters, long of stay in intensive care unit, APACHE II, SAPS and SOFA scores have been obtained for each participant. No gastrointestinal disease and malabsorption disorder has been detected in these patients. It has been confirmed that patients did not receive any vitamin supplementation prior admission to intensive care. Approval of the Gaziantep University Faculty of Medicine Ethics Committee has been obtain for this study (11-07-2019/307).

*Laboratory parameters*

Glucose, blood urea, blood creatinine, albumin, prealbumin, globulin and total protein levels are measured daily in this intensive care unit. These biochemical parameters and prognostic scales have been obtained from patients' files.

*Statistical analysis*

In this study, compliance of variables such as APACHE II, SAPS, SOFA scores and long of stay in ICU with normal distribution have been evaluated using histograms, variation coefficients, skewness, sharpness, detrended normality graph and Kolmogrov-Smirnov test. Mean ± standard deviation (SD) has been used to present descriptive statistics of variables with normal distribution. Median (IQR) has been used to present descriptive statistics of variables without normal distribution. The analysis of differences in continuous variables between two groups has been performed using Mann-Whitney U-test in cases which the data distribution is non-normal. Chi-square test has been used to compare frequency data in dependent groups. The Kaplan-Meier survival estimates have been calculated. The associations between continuous variables have been analyses using the non-parametric Spearmen correlation test in cases which the data distribution has been consistent with normal. IBM SPSS version 24 (IBM Corp., Armonk NY, USA) has been used for statistical analyses and calculations. Statistical significance level has been defined as $p<0.05$.

## Results

The mean age of the study population was 61.30±19.86. Gender distribution consists of 58.22%

**Table 1.** Comparison of patients groups about demographic data and biochemical parameters.

| | Group 1 | Group 2 | p |
|---|---|---|---|
| **Age (year)** | 67.36±16.96 | 56.66±20.64 | |
| **Sex, n (%)** | | | |
| **Men** | 80 (60.6) | 97 (56.4) | |
| **Women** | 52 (39.4) | 75 (45.6) | |
| **Glucose (mg/dL)** | 141(106/185) | 135.9(103/208.75) | 0.431 |
| **Urea (mg/dL)** | 85(51/165) | 58.45(32.70/119.12) | <0.001 |
| **Creatinine (mg/dL)** | 1.10(0.83/2.29) | 0.95(0.55/1.99) | 0.072 |
| **Albumin (g/dL)** | 2.44(2.20/2.70) | 2.89(2.44/3.25) | <0.001 |
| **Prealbumin (mg/dL)** | 7.30(3.90/8.85) | 7.35(4.62/11.98) | 0.008 |
| **Globulin (g/L)** | 67.36±16.96 | 2.93(2.51/3.40) | 0.001 |
| **Total protein (g/L)** | 5.10(4.60/5.70) | 5.82(5.21/6.50) | <0.001 |

men and 41.78% female. The mean age and gender distribution of patients by groups are given in table 1. The biochemical parameters of the patient groups during admission to intensive care unit are given in the table 1. The mean serum zinc level of the patients included in the study was 67.92±16.86. In addition, the mean serum zinc level was 74.93 ± 15.19 in patients under 65 years old and 72.20 ± 11.20 in patients over 65 years old. Serum zinc levels of the groups are given in table 2. Long of stay in ICU in group 1 and 2 were found median 9 (95% CI 7.53-10.47) and median 13(95% CI 9.75-16.25), respectively (p: 0.06).

## Discussion

Sepsis is a catabolic condition which the energy requirement increases. In order to fight against microorganisms, immune system response must be sufficient. Immune system cells need sufficient minerals and vitamins as well as energy requirement. Therefore, immune response may be impaired in the absence of molecules such as zinc which is not stored in the body. As far as known, present study is the most comprehensive zinc study in intensive care adult patients with sepsis. In this study, it is aimed to compared the levels of concentration of serum zinc in adult patients with sepsis and to explore their correlations with severity scores and clinic outcomes. The results have been reported in this study as follows: 1) There is a statistically significant difference between the groups in terms of 28 and 90-day mortality. 2) There is no difference between groups in terms of long of stay in intensive care unit. 3) It has been found that there is no difference between the groups in terms of APACHE II score, but there is a significant difference in terms of SAPS and SOFA scores. 4) SAPS and SOFA scores have been found lower in patients with normal serum zinc levels. 5) It has been found a statistically significant negative correlation between serum zinc level, SOFA and SAPS scores.

Sepsis, defined as life-threatening organ dysfunction due to irregular host response to infection, is a major health problem worldwide. The host's response

**Table 2.** Comparison of patient groups in terms of serum zinc level, long of stay in intensive care unit, 28 and 90-days mortality.

| | Group 1 | Group 2 | p |
|---|---|---|---|
| **Serum zinc level** | 51.80 ±14.97 | 82.16 ±9.78 | <0.001 |
| **Long of stay (day)** | 6(3/13) | 7(3/12) | 0.308 |
| **28-days mortality (%)** | 33.3 | 53.8 | <0.001 |
| **90-days mortality (%)** | 66.7 | 91.8 | <0.001 |

**Table 3.** Comparison of patient groups in terms of severity scores.

| | Group 1 | Group 2 | p |
|---|---|---|---|
| **APACHE II** | 16(12/23) | 14(11/21) | 0.081 |
| **SAPS** | 58(50/77) | 52(39/72) | 0.010 |
| **SOFA** | 11(7/16) | 9(5/14) | <0.001 |

**Table 4.** Correlations between severity scores, long of stay in intensive care unit and concentrations of serum zinc level.

| | Group 2 | p |
|---|---|---|
| **Serum zinc level- Long of stay in ICU** | 0.009 | 0.870 |
| **Serum zinc level- APACHE II** | -0.111 | 0.054 |
| **Serum zinc level- SAPS** | -0.232 | <0.001 |
| **Serum zinc level- SOFA** | -0.260 | <0.001 |

to an infection and trauma is called acute phase reaction (AFR). One of the properties of acute phase reactions is hypozincemia. In a study in which inflammatory response has been induced and healthy volunteers has been included, it has been found an increase in serum tumor necrosis factor alpha and interleukin 6 and a decrease in serum zinc concentration. The authors describe this situation as the entry on zinc into the liver by action of cytokines and synthesis of inflammatory molecules (11). Zinc is known to be essential to provide an appropriate immune response. Zinc is one of the essential trace elements for both pathogens and hosts (12). Zinc acts as a structural element for a large number of proteins as well as a cofactor for various enzymes (13). For production of inflammatory cytokines, redistribution of zinc from serum to liver occurs (14). As a result of this redistribution, synthesis of liver cytokines and acute phase reactants occur. There is a study showing an increased risk of sepsis in patients consistently low serum zinc level (15). There is also an animal study that it has been shown that zinc deficiency increases organ damage and mortality (16). Hence, the idea of high serum zinc levels in patients with sepsis makes sense. However, both 28 and 90-days mortality have been found higher in group 2 with normal serum zinc level during admission to the intensive care unit. Also, it does not have been found no significant difference between the groups in terms of long of stay in ICU. Both 28 and 90-days mortality in group 2 at admission to ICU has been found higher than group 1, indicating that zinc replacement did not have the expected effect on survival. A comprehensive meta-analysis recently published shows that antioxidant and trace element supplementation was associated with a significant reduction in overall mortality (17). But the studies included in the research were made with multiple trace elements and antioxidant molecules. Therefore, it does not mean the precise relationship between isolated zinc deficiency and its therapeutic use.

Studies about sepsis and zinc have often been performed in the neonatal period. There are not enough studies in adults about sepsis and zinc. In a meta-analysis published in 2017, it has been found that zinc supplementation reduce mortality rate but has no substantial influence on hospital stay (18). Mortality is a condition that may be affected by many factors. Factors such as heterogeneity of the patient population, applied treatments and procedures, available technological facilities, number of nurses and doctors per bed, qualified and equipped employees may efect the results. The conclusion is that the direct relationship between mortality should not be underlined by measure the serum zinc level during admission to ICU.

Disease severity scores are used to predict recovery from disease and to determine the severity of the disease and the degree of organ dysfunction. SAPS and APACHE II are used to physiological evaluation, while SOFA is used to evaluate organ dysfunction. In this study, all scoring parameters have been found higher in group 1 patients. But statistically difference has been found only with SAPS and SOFA scores. This difference may be due to lack of the hematocrit and respiratory rate parameters not used in SAPS but used in APACHE II scoring (19). Because respiratory system is one of the first affected systems in patients with sepsis and tachypnea may be the first finding. Decrease in hematocrit level may cause tachypnea due to insufficiency of oxygen supply to tissues. In the light of these findings, low serum zinc level at admission to intensive care is associated with scoring systems especially with SOFA and SAPS. And this relationship has been found to be statistically significant with the negative correlation found in this study.

## Conclusion

It seems that there is no positive effect of zinc replacement at daily dose of metabolism requirement on mortality of patients with sepsis in ICU and is no statistical significance with APACHE II score. Further and comprehensive randomized controlled trials are needed to investigate the effect of zinc replacement on mortality over daily requirement doses in patients with sepsis.

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