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Original Research Article

Could plasma zinc be a predictor for mortality and severity in sepsis syndrome?

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ABSTRACT

Background: While many factors are known to play a role in outcomes of sepsis, the role of micronutrients such as zinc remains a gray area. This study assesses the correlation of plasma zinc levels with mortality and severity of sepsis. Objective was to study the association between plasma zinc levels with mortality and severity of sepsis.
Methods: Comparative prospective observational study which included 89 patients with proven sepsis according to the society of critical care medicine (SCCM) guidelines. The study was conducted at a tertiary care centre in South India. A total of 89 patients who were admitted into the medical ICU directly from ER, from December 2014 to August 2015 were chosen for the study after satisfying specific inclusion criteria and divided into 2 outcome groups based on mortality.
Results: There was a significant association between plasma zinc (categorized as low, normal and high plasma zinc) and outcome. While the severity of sepsis as per SOFA score on admission did not have an association, there was a significant association between plasma zinc and the 48-hour SOFA score.
Conclusions: Higher plasma zinc values had lower mortality and lower 48 hours SOFA score, strengthening the hypothesis regarding the role of zinc in the immune response to sepsis. More research is needed regarding the role of zinc in assessing the severity and predicting the mortality of patients with sepsis.

Keywords: Mortality, Severity of Sepsis, Sepsis, SOFA, Zinc

INTRODUCTION

Zinc is an essential micronutrient whose biological function in the human body is diverse. As a trace element, it is indispensable, both structurally and functionally, for the proper functioning of many key biological enzymes.[1,2] The typical concentration of zinc in the body is about 2 to 4 grams which is mostly concentrated in the brain, muscle, bones, kidney and liver. It is the second most abundant transition metal in the human body after iron and is the only metal which appears in all the different enzyme classes.[3] Zinc is also a key component of several transcription factors essential for cellular function and plays a role in enhancing cellular defence during states of acute stress and chronic inflammation.[4-6]

Zinc plays an important role in the development and normal functioning of the immune system as well, especially cell-mediated immunity. Neutrophils, natural killer cells and macrophages all require zinc for normal development and function.[7,8] Evidence suggests that zinc deficiency adversely affects immune function by impairing chemotaxis and immunity.[9] Induced deficiencies in mice have been shown to cause thymic atrophy along with reduction in splenocytes and

attenuated responses to both T-cell-dependent and independent antigens.[10] Decrease in cytosolic zinc levels has also been observed to potentiate activation of apoptosis. An impairment of the various functions of zinc due to deficiency thus begins at the cellular level and contributes to considerable dysfunction at the tissue level.

As with any other nutrient, zinc consumption and assimilation is prone to deficiency due to various reasons including socio-economic status and dietary habits. Wessells and Brown in 2012 published a study estimating the global prevalence of zinc deficiency which placed an estimated 17.3% of the global population being at risk of inadequate dietary zinc intake. The regional estimated prevalence of inadequate zinc intake ranged from 7.5% in high-income regions to 30% in South Asia with high prevalence in Sub-Saharan Africa and South Asia.[11] High prevalence of deficiency was also found amongst specific demographics in Latin America suggesting many potential etiologies especially diet, age and socio-economic status.[12]

Infections leading to sepsis are common in India given the burden of communicable diseases and other healthcare related challenges. An epidemiological study based in India showed ICU mortality in sepsis was 12.08% and 59.26% in severe sepsis.[13] Our understanding of sepsis and the mechanisms behind this condition continue to evolve since the first international consensus on sepsis in 1991.

Even the definition of what constitutes sepsis continues to evolve with an international task force this year revising the definition of sepsis to, 'A life-threatening organ dysfunction due to a dysregulated host response to infection.'[14] Similarly, strides in the pathophysiology and treatment of sepsis continue to surface as research progress. One of these areas of progress includes trace elements and their role in sepsis. Given the array of evidence that suggests a dysfunctional immune response in the face of zinc deficiency, it is prudent to anticipate poor outcomes in infections. There have been many studies investigating the role of zinc in neonatal sepsis with evidence suggesting improved outcomes with supplementation.[15,16]

However, literature evaluating such a role in adults with sepsis is lacking and a systematic review of literature on Medline indexed sources revealed the same. Hence, this pilot study was undertaken with the prime objective of evaluating plasma zinc as an independent factor in the mortality, severity and the length of ICU stay in patients with sepsis.

METHODS

This study was a comparative prospective observational study that was carried out over a 9-month period from December 2014 to August 2015 at a tertiary care centre in south India. The study was designed to include subjects who were admitted into the medical ICU directly from the emergency room (ER). 89 patients were enrolled after satisfying specific inclusion criteria and the outcome groups contained 47 and 42 patients in the expired and alive groups respectively.

Sepsis was defined as per the guidelines established by the society of critical care medicine (SCCM) at the time of the study. The study included all patients above the age of 18 who were diagnosed with sepsis and admitted to the ICU for the same. Patients with positive histories of malabsorptive syndromes or those having recently consumed vitamin/nutritional supplements were excluded from enrolment. Only direct admissions into the ICU, meeting the above inclusion and exclusion criteria were chosen for the study. Ethical clearance to conduct the study was obtained from the institutional ethics committee.

The patients' basic clinical parameters were noted, routine investigations were sent as per standard of care and SOFA scores were calculated. SOFA scores of 9 and above were considered high and those below 9 were classified as low. Plasma zinc was measured on admission by inductively coupled plasma atomic spectrometry. Early goal-directed therapy as per standard of care, without bias, was administered to both study groups.

Statistical analysis

Data was collected, organized and prepared for analysis using Excel and core data analysis was performed using SPSS v22. Basic analyses such as mean and standard deviation were performed along with other tests viz; Chi Square, Correlation, T-test and ANOVA tests.

RESULTS

In the study population, demographics, comorbidities and foci of sepsis were analyzed statistically to determine differences in the incidence of various factors between the two groups as represented in Table 1.

Amongst the expired group, the mean serum zinc value was 83.83 pg/ml with a standard deviation of 13.35 pg/ml and amongst the alive group the mean plasma zinc value was 86.881 pg/ml with a standard deviation of 14.64 pg/ml. The difference in the plasma zinc values was compared between the two groups with the t-test and was found to be not significant ($p = 0.307$).

The normal reference range of plasma zinc is 70 to 110 pg/ml. The study population was further classified into three categories of low, normal and high plasma zinc levels based on whether the values were below 70 pg/ml, between 70-110 pg/ml and above 110pg/ml respectively; which was then compared with the primary outcome of mortality via the Chi Square test and found to be statistically significant ($p = 0.001$). 19 of the 22 patients

(86.4%) with low plasma zinc expired, 24 out of 40 (60.0%) with normal zinc values expired, while only 4 out 27 (14.8 %) patients with high plasma zinc level expired as listed in Table 2.

Table 1: General patient characteristics in the expired and alive groups with their corresponding p-values.

	Expired	Alive	p-value
Total number	47	42	
Age (years)	61.33±16.33	61.83±12.35	p = 0.45
Sex			
Males	33	24	p = 0.199
Female	14	14	
Co-morbid conditions			
Type 2 diabetes mellitus	26	19	p = 0.342
Hypertension	26	21	p = 0.616
Coronary artery disease	12	9	p = 0.649
COPD	8	4	p = 0.301
Chronic liver disease	9	8	p = 0.990
Hypothyroidism	3	5	p = 0.318
Focus of sepsis			
Respiratory tract infection	18	16	p = 0.984
Cellulitis	6	9	p = 0.541
Urinary tract infection	18	22	p = 0.814
Meningitis	2	7	p = 0.053
Abdominal focus of sepsis	7	0	p < 0.001
Other focus of sepsis/ sepsis of unknown origin	7	1	p = 0.363

Table 2: Patients in the alive and expired groups based on their plasma zinc level.

Plasma zinc level	Number of patients	Number of patients who expired	Mortality %
Low (<70 pg/ml)	22	19	86.4%
Normal (70 – 110 pg/ml)	40	24	60.0%
High (>110 pg/ml)	27	4	14.8%

The zinc values categorized as low, normal and high plasma zinc levels were compared with SOFA scores, which were obtained at admission and 48 hours later. This comparison was performed using the Chi Square test. While no association was found between the plasma zinc range and the SOFA scores obtained at admission, there did exist a significant association between the plasma zinc and the 48-hour SOFA score (p = 0.005). Lower plasma levels of zinc were seen associated with higher SOFA scores at 48 hours as described in Table 3.

To further explore any correlation between the plasma zinc and the systemic inflammatory response in sepsis, correlation between plasma zinc and various acute phase reactants were studied. No association was found between plasma zinc and the total WBC count, however, a positive correlation between plasma zinc values and CRP. Association between plasma zinc and length of ICU stay was analyzed using the ANOVA test and no association was found (p = 0.984).

The biological role of zinc is protean and its role in infections is well studied. No statistical differences in the outcomes were evident between the expired and live groups' demographics, co-morbid conditions and foci of sepsis except in the case of patients who had an abdominal focus of sepsis.

A significant association was observed between the range of plasma zinc and outcome. As evidenced by the results of the study, the group of patients who had higher plasma zinc values had a lower incidence of mortality. However, no significant association was found between plasma zinc and length of ICU stay.

The statistically significant association between plasma zinc value and the SOFA score obtained 48 hours after admission suggests a more attenuated and controlled immune response to Sepsis. This hypothesis has further validated the negative correlation observed between acute phase reactants like CRP and plasma zinc levels.

Table 3: SOFA scores of the patients based on their plasma zinc level.

Plasma zinc level		48 hour SOFA score		Total	p value
		Low (<9)	High (>/=9)		
Low (<70 pg/ml)	Number	4	18	22	<0.001
	Percentage	18.2%	81.8%	100%	
Normal (70-110 pg/ml)	Number	19	21	40	
	Percentage	47.5%	52.5%	100.0%	
High (>110 pg/ml)	Number	23	4	27	
	Percentage	85.2%	14.8%	100.0%	
Total	Number	46	43	89	
	Percentage	51.7%	48.3%	100.0%	

DISCUSSION

Zinc is an active component of over hundreds of biochemical enzymes in the human body. Our dietary sources of zinc are primarily from animal products including meat, milk and seafood while cereals are the major plant derived source. Zinc absorption occurs mainly in the small bowel and most of it is bound intracellularly to metalloproteins. Absorption is hampered by presence of high fiber content and phytates in food.[15]

Dietary deficiency is the major cause of zinc deficiency which is especially prevalent in developing countries such as in Sub-Saharan Africa and South Asia.[11] It is also interesting to note that mortality associated with sepsis is significantly more in such low income countries.[16] This significant overlap between the zinc deficient nations and countries with poorer sepsis related outcomes raises the question of whether or not zinc plays a role amongst several other factors in determining the outcome related to sepsis.

In scenarios where fortified foods are unavailable, especially during the weaning period in infants, supplementing with meats can avoid any zinc deficiency.[17,18] Less common causes of zinc deficiency include Acrodermatitis enteropathica, Crohn disease, Cystic fibrosis, Sickle cell disease, chronic liver and kidney diseases. Patients on total parenteral nutrition (TPN) following bowel resection who do not receive supplemental zinc are also at risk for developing clinical features of zinc deficiency or hypozincemia. Zinc is one of the FDA approved trace elements that is included in home parenteral nutrition (HPN) in patients on TPN.[19]

Clinical features of hypozincemia are very nonspecific and may range from altered smell and taste, night blindness and mild diarrhea to chronic lethargy, impaired immunity leading to frequent infections, dermatitis and alopecia.[20-22] Sepsis is a state of high oxidative stress and the host response is usually through inflammation which occurs by activation of inflammatory mediator expression following gene activation which is often exaggerated in this state.[23] The exact point when the host response crosses the line from function (adaptive response) to dysfunction (maladaptive response) is arbitrary. The monocyte/tissue macrophages bind to the components of the bacterial cell wall via unique receptors on their surface resulting in the activation of the inflammatory and coagulation cascades. Since these pathways are interlinked, their activation leads to further amplification of the host response. As zinc plays a significant role in these steps, it is possible that it can measure the degree of this inflammatory cascade.

The role of zinc as an antioxidant is very well known and has been studied extensively in the past.[24,25] There is evidence in literature that zinc and selenium concentrations declined in patients with sepsis, probably owing to the high oxidative stress associated with this condition. This may in turn lead to damage of several key proteins which may play a major role in combating this high oxidative stress environment.[26] When faced with a stressor for example an infection, the host defence mechanism is designed to increase cellular bioavailability of zinc for cytoprotective functions like protein synthesis, neutralization of reactive oxygen species, and prevention of microbial invasion. Multiple studies have shown that phagocytosis, intracellular killing and cytokine production are all impaired by zinc deficiency.[20]

A study by Ji Young Jang et al showed that the serum zinc level was profoundly lower in patients with sepsis compared to patients with trauma indicating that it may be due to mechanisms other than being used up to combat the high oxidative stress environment as this is a common denominator in both sepsis and trauma.[27] The following is a summary of literature regarding the role of zinc in other infectious syndromes;

- Choi et al have studied the role of microelements in mycobacterial tuberculosis and it was found that low plasma zinc was associated with poorer outcomes and higher mortality.[28]
- Alieva et al have shown that in purulent skin infections, low serum zinc was an independent factor associated with delayed wound healing.[29]

- Beneficial effects of zinc supplementation in treatment of shigellosis was shown by Muhammad et al.[30]
- Lower serum zinc levels were observed in patients with cutaneous, mucosal and visceral leishmaniasis as shown in a study by Overbeck et al.[31]
- A study by Takeshi et al shows how low plasma zinc levels are associated with a less sustained immune response to malaria.[32]
- Lai et al have shown the role of plasma zinc as well as plasma copper: zinc ratio as a predictor of survival in patients with HIV-1 infection.[33]

The role of plasma zinc in neonatal and paediatric sepsis has been well studied and documented with two randomized controlled trials.[34,35] These studies suggest better outcomes in children with the sepsis syndrome who were supplemented with zinc.[16]

The role of zinc as an all-cause mortality predictor in the elderly by Malavolta et al with positive outcomes.[36] The therapeutic benefits of zinc supplementation in reducing incidence of pneumonia, as well as augmenting T-cell response in elderly have been studied previously.[37,38] Interventional studies by supplementing zinc and other micronutrients has been shown to improve the outcome in critically ill patients as well.[5]

Sepsis is a global burden responsible for about 56-91 cases per 100 000 people with about 30% mortality annually and is one among the top ten causes of death worldwide.[39] Over the years, strides have been made in various aspects of its diagnosis and management along with enhanced clarity in its pathophysiological profile; although there remain avenues to be explored. The role of trace elements and zinc is one such avenue that invites more investigation. A study by Helmy et al suggests that low zinc levels is one among several other predictors of sepsis.[40]

In addition to exploring the significance of zinc as a mortality predictor in sepsis, we need to know if there would be any benefit in correcting hypozincemia in patients with sepsis syndromes. Even though the confounding variables are several, the results of present study reflect a strong negative correlation between plasma zinc level and the SOFA scores and the mortality associated with sepsis.

One of the important limitation is that the follow up of patients after shifting out of the ICU was not done, therefore an all cause hospital mortality was not considered in this study. Another limitation is that only Meningeal and Abdominal foci have a statistically significant association the primary outcome of mortality in this study. Larger studies may be needed to ascertain the role of plasma zinc in these conditions. However, this study should pave the way for more research, as it opens several possibilities regarding the effect of zinc not only as a marker of inflammation but also as a predictor of severity and the mortality in patients with the sepsis syndrome as well as its potential benefits in a state of sepsis if supplemented.

CONCLUSION

Higher plasma zinc values had lower mortality and lower 48-hour SOFA score strengthening the hypothesis of the role of zinc in the immune response in sepsis syndrome. More research is needed regarding the potential use of zinc as a mortality predictor in sepsis, or integrating it with the existing severity predictors. We also need larger interventional studies to assess the effects of correcting zinc deficiencies early on in sepsis.

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