International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Profile of Serum Zinc Levels in Pediatric Sepsis Patients at Pediatric Intensive Care Unit Sanglah Hospital Denpasar - Bali

Defranky Theodorus[1], Dyah Kanya Wati[2], Ida Bagus Gede Suparyatha[3], I Nyoman Budi Hartawan[4]

[1, 2, 3, 4]Udayana University, Medical Faculty, Department of Child Health, Sanglah Hospital, Denpasar, Indonesia
dokter_franky[at]yahoo.com

Abstract: ***Introduction: Low serum zinc levels are associated with immune dysfunction, morbidity and mortality due to sepsis. Decreased serum zinc levels are associated with disease's severity and mortality. Low serum zinc levels often undetected and are not considered during treatment in the pediatric intensive care unit. In Indonesia there has been no research on serum zinc levels in pediatric sepsis patients. Purpose: To know the prevalence and characteristics of serum zinc levels in pediatric sepsis patients at the pediatic intensive care unit (PICU) of the Sanglah Hospital Denpasar in 2019. Methods: This research was a prospective descriptive study, which used PELOD-2 score for diagnosing sepsis in pediatric patient and determination of serum zinc levels through venous blood tests at the pediatric intensive care unit Sanglah Hospital which was collected using the consecutive sampling method with inclusion and exclusion criteria. Results: Total of 56 children diagnosed with sepsis were included in this study. Infant age group is the largest age group suffering from sepsis, accounted for 44.6%. The mean zinc content was 62.0 ± 28.97 with a low zinc level of 69.7% and the death was 25%. Higher PELOD-2 score means lower zinc levels, with the comparison of PELOD-2 scores > 7 and > 11 are 16.1% and 53.6%, respectively. Conclusion: Low serum zinc levels were found in septic patients and correlates with organ failure.***

Keywords: Serum zinc level, sepsis, pediatric intensive care unit

1. Introduction

Sepsis is a major cause of morbidity and mortality in children with critical illnesses who are admitted to intensive care units [1]. Sepsis is one of the leading causes of death worldwide, which accounted for 6 million deaths per year [2]. Multiple organ dysfunction syndrome is a marker of the severity of a disease and is the main cause of death in the pediatric intensive care unit (PICU) [3]. At PICU Cipto Mangunkusumo Hospital, which is a national referral center, 19.3% of 502 pediatric patients are treated with sepsis with a mortality rate of 54% [4]. At PICUSanglah Hospital Denpasar in 2018 the prevalence of children experiencing sepsis at the age of 0 years to 18 years was 35.7% with a mortality rate of 30% [1]. Critically ill patients experience severe stress, inflammation and clinical conditions that increase the utilization and replacement of metabolism many nutrients, especially zinc [5].

Zinc is an important element that plays a role in many biological functions, including mucosal barrier function, innate and adaptive immunity, responses to oxidative stress and cofactors to various enzymes. Trace element especially zinc are the basic of the antioxidant defense in the acute systemic inflammatory response syndrome (SIRS). SIRS is associated with zinc' redistribution to tissues involved in protein synthesis and proliferation of immune cells, leading to decreased serum zinc levels [6]. In the early stages of sepsis, the rapid release of cytokines activates the acute phase response especially in the liver leading to acute phase protein production [7]. Zinc levels serum decreases rapidly after redistribution from plasma to tissue and called hyposengsemia[8]. Pathogens use zinc as a transport with high affinity so that the beneficial role of hyposengsemia is to limit zinc availability as a defense mechanism against infection. Zinc works as a nutritional immunity to fight infection [9].

Several studies in the last decade have shown decreased zinc levels in sepsis patients. Besecker et al.,reported a decrease in serum zinc levels treated in the intensive care unit compared to non-sepsis critically ill patients [10]. Lower plasma zinc concentrations and higher SLC39A8 mRNA expression correlated with increased disease severity. Helmy and Beshey[11] found that low serum zinc levels can be a predictor of death in septic patients. Hoeger et al.,showed that low serum zinc levels in surgical sepsis patients are associated with a higher risk of recurrent sepsis episodes and higher mortality rate [12]. Florea et al.,showed that changes in zinc levels were associated with disease severity in critically ill patients in the intensive care unit [5]. Wati et al.,found there were significant correlation in TNF-α and IL-6 measurement between zinc plasma insufficiency with pro-inflammatory cytokines in the first 24 hours and significant correlation in TNF-α in 72 hours[13].

Low zinc levels in the blood are influenced by several factors. Prasad et al were the first to report zinc deficiency in humans. Since then zinc deficiency has been identified in many clinical conditions such as acrodermatitis enteropathica, kwashiorkor, celiac disease, cystic fibrosis, and inflammatory bowel disease as well as in patients receiving long-term parenteral nutrition without zinc supplementation [14]. Increased metabolic activity induces decreased zinc levels. Several conditions can affect serum zinc levels such as diabetes mellitus, cardiovascular disease and anemia due to acute blood loss and liver diseases [15]. Zinc levels in chronic hepatic patients are lower than in healthy control subjects. The zinc levels in patients with hepatic cirrhosis and hepatocellular carcinoma were significanly lower than in the chronic hepatitis group [16]. During the acute phase of fever, including gastroenteritis, infection and exposure to endotoxins or cytokines cause serum zinc levels to decrease. Acute diarrhea can lead to decreased serum zinc levels [17].

Low serum zinc levels are associated with immune dysfunction, morbidity and mortality due to sepsis. Decreased serum zinc levels are associated with disease severity and mortality. Low serum zinc levels often go undetected and are not considered during treatment in the pediatric intensive care unit. In Indonesia there has been no research on serum zinc levels in pediatric sepsis patients. Currently, the profile of serum zinc levels in children with sepsis at PICU Sanglah Hospital Denpasar - Bali is not known. Based on this, the authors consider the importance of knowing the profile of serum zinc levels in pediatric sepsis patients at the Sanglah Hospital Denpasar - Bali.

2. Methods

We perform a cross-sectional prospective study using a descriptive design that examined the profile of serum zinc levels in pediatric patients at PICU Sanglah Hospital Denpasar – Bali from January - Desember 2019. Diagnosis of sepsis based on the calculation of PELOD-2 score. To see the serum zinc level, 5 ml of venous blood was taken and then the examination was carried out using ICP-MS elements. The sepsis diagnosis was made if the PELOD-2 score is more than or equal to seven. The inclusion criteria in this study were pediatric patients aged 29 days-18 years with sepsis based on the PELOD-2 score who were treated at PICU Sanglah Hospital in Denpasar and their parents were willing to participate in the study and sign the informed consent. Patients with acute diarrhea, severe malnutrition, acrodermatitis enteropathica, inflammatory bowel disease, diabetes mellitus, and liver disease (chronic hepatitis, hepatic cirrhosis, and hepatocellular carcinoma) were excluded from this study. Sampling was done by consecutive sampling technique. The sample size was calculated using the sample calculation formula for categorical descriptive data and the minimum required sample size was 56 subjects. The variables in this study is serum zinc level is the zinc level which is determined by the result of venous blood examination using the ICP-MS trace element method. Normal zinc level if the serum zinc level is in the range 70-158 µg/dL, low if the serum zinc level is below 70 µg/dL and high if the serum zinc level is above 158 µg/dL [19]. Sepsis if the PELOD-2 score $\geq$ 7. Gender, age, nutritional status, length of stay in PICU, exclusive breastfeeding, origin, procalcitonin, and Outcome.

All data collected were analyzed with a computer program. Categorical variables are described in number (n) and percentage (%) and are presented in tabular form.

This research has obtained a statement of ethical suitability from the Ethics Committee of the Research and Development Unit (Litbang) of the Faculty of Medicine, Udayana University/ Sanglah Hospital Denpasar.

3. Result

Data collection resulted in 56 subjects during the study period January 2019- December 2019 with a diagnosis of sepsis based on PELOD-2 criteria who met the inclusion and exclusion criteria who were treated at PICU Sanglah Hospital Denpasar. The characteristics of the research subjects can be seen in Table 1.

Table 1: Sample characteristics

Characteristics	N=56
Mean zinc serum level, (SD)	62,0 ± 28,97
Serum Zinc Level, n (%)	
Low	39 (69,6)
Normal	17 (30,4)
Sex, n (%)	
Male	25 (44,6)
Female	31 (55,4)
Group age, n (%)	
Infant	25 (44,6)
Toddler	11 (19,6)
Children	14 (25,0)
Adolescent	6 (10,7)
Nutritional status, n (%)	
Over weight	10 (17,9)
Well nourished	20 (35,7)
Under weight	26 (46,4)
Leng of stay in PICU, n (%)	
<7 days	9 (16,1)
7 - 14 days	39 (69,6)
>14 days	8 (14,3)
Exclusive breastfeeding, n (%)	
Yes	26 (46,4)
No	30 (53,6)
Origin, n (%)	
Rural	42 (75)
Urban	14 (25)
Procalcitonin, n (%)	
High	54 (96,4%)
Low	2 (3,6%)
Outcome, n (%)	
Dead	22 (39,3)
Alive	34 (60,7)

Table 1 shows the distribution of the sample characteristics. The low serum zinc level in sepsis was 69.6%. The distribution of sexes for both men and women is not different significanty. In the age category, the age variable is categorized into several classifications, (1) infant (<2 years); (2) toddlers (2-5 years); (3) children (5-12 years); (4) adolescents (> 12 years). The infant age category was the highest in the sample, 44.6%. 39.3% of the patients who died.

Table 2: Serum zinc level's distribution according to sample

Characteristics	Zinc level		N=56
	Low (N=39)	Normal (N=17)	
Sex, n (%)			
Male	18 (32)	7 (12,5)	25 (44,6)
Female	21 (37,5)	10 (17,9)	31 (55,4)
Age group, n (%)			
Infant	16 (28,6)	9 (16,1)	25 (44,6)
Toddler	8 (14,3)	3 (5,4)	11 (19,6)
Children	11 (19,6)	3 (5,4)	14 (25,0)
Adolescent	4 (7,1)	2 (3,6)	6 (10,7)
Nutritional status, n (%)			
Over weight	8 (14,3)	2 (3,6)	10 (17,9)
Well nourished	15 (26,8)	5 (8,9)	20 (35,7)
Under weight	16 (28,6)	10 (17,9)	26 (46,4)
Leng of stay in PICU, n (%)			
<7 days	7 (12,5)	2 (3,6)	9 (16,1)
7 - 14 days	28 (50,0)	11 (19,6)	39 (69,6)
>14 days	4 (7,1)	4 (7,1)	8 (14,3)

Exclusive breastfeeding, n (%)			
Yes	19 (33,9)	7 (12,5)	26 (46,4)
No	20 (35,7)	10 (17,9)	30 (53,6)
Origin, n (%)			
Rural	31 (55,4)	11 (19,6)	42 (75,0)
Urban	8 (14,3)	6 (10,7)	14 (25,0)
Outcome, n (%)			
Dead	14 (25,0)	8 (14,3)	22 (39,3)
Alive	25 (44,6)	9 (16,1)	34 (60,7)
Procalcitonin, n (%)			
High	37 (66,1)	17 (30,4)	54 (96,4)
Low	2 (3,6)	0 (0,0)	2 (3,6)
PELOD 2 score, n (%)			
≥ 7	9 (16,1)	6 (10,7)	15 (26,8)
≥ 11	30 (53,6)	11 (19,6)	41 (73,2)

The distribution of zinc levels based on sample characteristics is listed in Table 2. There were no high serum zinc levels found in septic patients. Low serum zinc levels in septic patients were more common in women than men (37.5% vs 32.1%) and the age group with Low serum zinc levels were mostly found in infants (28.6%). The group that did not receive exclusive breastfeeding, and died sample had low serum zinc levels, respectively (35.7% vs 25.0%). The distribution of zinc levels based on the highest PELOD-2 score with low serum zinc levels was found at PELOD-2 score> 11 (53.6%) compared to PELOD-2 score > 7 (16.1%).

4. Discussion

Assessment of organ dysfunction/failure in children uses several scoring systems, including Pediatric Multiple Organ Dysfunction Score (P-MODS), Pediatric Logistic Organ Dysfunction (PELOD), Pediatric Logistic Organ Dysfunction-2 (PELOD-2), and the Pediatric Sequential Organ Failure Assessment (pSOFA) system adapted from the

Sequential Organ Failure Assessment (SOFA) system with validation results showing that pSOFA provides the same good results as other scoring systems. In Indonesia, PELOD-2 is an organ dysfunction assessment system recommended by the Indonesian Pediatric Association in diagnosing sepsis in children. The diagnosis of sepsis is made when the PELOD-2 score is ≥11 (in type A hospitals), or ≥7 in type B or C health services [27].

In our study, 56 children were diagnosed with sepsis based on PELOD-2 score, with criteria for PELOD-2 score >7 (26.8%) and PELOD-2 >11 (73.2%) with the infant age group being the largest age group (44.6%), and the largest gender was female (55.4%). Overall, 39.3% of subjects with outcome died. Our research is similar to the research conducted by Wati et al.,using pSOFA in 2018 at PICU Sanglah Hospital Denpasar, where in this study, sepsis in the infant age category was the highest (57.1%) and female gender accounted for (56%) with a death outcome of 39.3% [1]. Different results on sex and death outcomes are shown by Dewi and Fatimatuzzuhroh [20], at PICU Cipto Magunkusumo Hospital (RSCM). In that study, the 1-11 month age category was the largest subject (27.9%) of the other age groups, but in terms of gender the results were inversely proportional, where there were more men than women (56.4% vs 43.4%) and mortality rate was lower than our study (10.7%). This difference may be due to the larger number of the study sample in that study and the different classification of age categories.

Low serum zinc levels in critically ill patients treated in intensive care rooms [5],[10],[11],[12],[28]. Cvijanovich et al., at the PICU of Children's Hospital and Research Center Oakland ,obtained a median value of 2.9 years with male are the dominant sex at 55% [28]. These results are in accordance with our study where the median age value is 2.4 years but different in gender where our study was found more in female subjects by 37.5%. The study said serum zinc levels were low regardless of age, sex, or diagnosis.

The mean serum zinc level of septic patients in our study was 62 $\pm$ 28.9. Our results were lower than Besecker et al., at the ICU of Ohio State University Medical Center, whose serum zinc levels were 45.5 $\pm$ 18.1 below normal in septic patients [10]. This difference is mainly due to the number of samples and diseases that can affect the low zinc levels. In sepsis, there is a change in zinc homeostasis in the blood. The presence of pathogens increase production of inflammatory cytokines (tumor necrosis factor-α, interleukin 6, and interleukin 1β) which results in increased imports of zinc and metallothionein in the liver resulting in redistribution of zinc from serum to liver. The decrease in serum zinc levels, stimulates the immune system and the process of monocyte maturation, while the increase in liver zinc levels will lead to cytokine production, acute phase protein production and as protection of liver tissue [29].

Visalakshy et al.,at ICU of a tertiary care centre in south India found higher serum zinc levels associates with lower mortality, in that study 86.4% died with low serum zinc levels, 60.0% died with normal zinc levels and 14.8% died with normal zinc levels. zinc is more than normal value [30]. Our study is consistent with these findings but our results were lower, where 25% of subjects died with low zinc levels, and 14.3% with normal zinc levels, and no high serum levels were found in sepsis patients. This difference was mainly due to samples with diseases that could predispose to low zinc levels were excluded in our study.

In this study zinc levels were inversely related to organ failure scores. The higher the organ failure score, the lower zinc levels. These results are consistent with the findings of Cvijanovich et al.,who reported low zinc levels as inversely related to the degree of organ failure [28] , and the findings of Linko et al.,who found an association between low zinc levels and organ failure scores [31]. Similar results were reported by Negh et al.,at the PICU of Benha University Hospital, foundserum zinc concentrations were decreased in critically ill children with organ dysfunction during sepsis [32].

Several studies have shown an association between serum zinc concentrations and organ failure due to inflammatory or septic responses. In critically ill patients with high organ failure scores showed significantly lower serum zinc concentrations than patients with low organ failure scores, where a higher organ failure score was associated with higher mortality [5],[33]. In line with these results, serum

zinc concentrations were found to be inversely correlated with organ failure scores in other studies [10],[34]. Other studies revealed significantly lower serum zinc concentrations in septic patients who developed recurrent sepsis compared with those who did not experience recurrent sepsis. In addition, subjects who died from sepsis had significantly lower serum zinc concentrations than those who survived [35]. Serum zinc levels play a major role in many important functions in the body, especially the immune system, so this relationship becomes important that decreased serum zinc levels contribute against some side effects, thus exacerbating the state of sepsis [29].

This research has several limitations. First, this is a descriptive study that cannot analyze the relationship between the variables studied. The number of samples in this study is relatively small, so further research is needed with a different research design and a larger number of samples. Second, the study sample was only drawn from one hospital, so it cannot be representative of the population of children with sepsis. We hope that this study can become the basic for further research on serum zinc levels in pediatric sepsis patients on a larger scale. In addition, the assessment of serum zinc levels is only assessed at one time, so it cannot be measured the decrease in serum zinc levels in the course of sepsis. Determination of the diagnosis of sepsis using the PELOD-2 score includes PELOD score >7 which this study was conducted in a tertiary hospital. The reason for this is due to limited time and research samples. This study did not look at a comparison in patients who were not septic, so there was no comparison between zinc levels in septic and non-septic patients.

In conclusion, low serum zinc levels were found in septic patients and the lower zinc's serum associated with higher organ failure score.

References

[1] Wati DK, Hartawan INB, Suparyatha IBG, Mahalini DS, Pratiwi IGAPE, Utama IMGDL. Sari Pediatri 2019;21(3): 152-8.
[2] World Health Organization. 2017. Improving the prevention, diagnosis and clinical management of sepsis. https: //www.who.int/sepsis/en/. 2 January 2019 (20:20).
[3] Proulx F, Joyal JS, Mariscalco MM, Leterurtre S, Leclerc F, Lacroix J. The pediatric multiple organ dysfunction syndrome. Pediatr Crit Care Med 2009;10:12–22.
[4] Ikatan Dokter Anak Indonesia. 2016. Diagnosis dan tatalaksana sepsis pada anak. Badan penerbit Ikatan Dokter Anak Indonesia.
[5] Florea D, Lopez JM, Hogstrand C, Lengyel I, Cruz AP, Rodriguez-Elvira M, dkk. Changes in zinc status and zinc transporters expression in whole blood of patients with Systemic Inflammatory Response Syndrome (SIRS). J. Trace Elem. Med. Biol 2017; 1-8.
[6] Saleh NY, Fotoh WM. Low serum zinc level: The relationship with severe pneumonia and survival in critically ill children. Int J Clin Pract 2018; 1-9
[7] Quinton LJ, Blahna MT, Jones MR, Allen E, Ferrari JD, Hiliard KL, dkk. Hepatocyte-specific mutation of both NF-kappaB RelA and STAT3 abrogates the acute phase response in mice. J Clin Invest 2012;122: 1758–63.
[8] Moshage H. cytokines and the hepatic acute phase response. J Pathol 1997;181: 257-66.
[9] Kehl-Fie TE, Skaar EP. Nutritional immunity beyond iron: a role for manganese and zinc. Curr Opin Chem Biol 2010;14:218-24.
[10] Besecker BY, Exline MC, Hollyfield J, Phillips G, DiSilvestro RA, Wewers MD. A comparison of zinc metabolism, inflammation, and disease severity in critically ill infected and noninfected adults early after intensive care unit admission. AM J Clin Nutr 2011;93: 1356-64.
[11] Helmy TA, Beshey BN. Correlation between serum zinc and mortality in septic patients. Int J Adv Res 2016;4: 1514-17.
[12] Hoeger J, Simon TP, Beeker T, Marx G, Haase H, Schuerholz T. persistent low serum zinc is associated with reccurent sepsis in critically ill patients - A pilot study. Plos ONE 2017;12(5): 1-10.
[13] Wati DK, Sidiartha L, Tunas K, Setiawan A. Correlation between zinc plasma level to inflammation response of patient with ventilator in pediatric intensive care unit. Cirtical Care and Shock 2019;22: 161-71.
[14] Naveh Y, Lightman A, Zinder O. Effect of diarrea on serum zinc concentration in infants and children. Pediatr 1982;101(5): 730-32.
[15] Davies IJ, Musa M, Dormandy L. measurements of plasma zinc. J Clin Path 1986;21: 359-65.
[16] Moriyama M, Matsumura H, Fukushima A, Ohkido K, Arakawa Y, Nirel K, dkk. Clinical significance of evaluation of serum zinc concentration in C-viral chronic liver disease. Dig Dis Sci 2006;51: 1967-77.
[17] Olmez A, Yalcin SS, Yurdakok K, Coskun T. Serum zinc levels in children with acute gastroenteritis. Pediatr Int 2007;49: 314-17.
[18] Linko R, Karlsson S, Pettila V, Varpula T, Okkonen M, Lund V, dkk. Serum zinc in critically ill adult patients with acute respiratory failure. Act Anaesth Sca 2011;55: 615-21.
[19] Dehgani SM, Katibeh P, Haghighat M, Moravej H, Asadi S. Prevalence of zinc defisiency in 3 – 18 years old children in Shiraz-Iran. Iran Red Cresc Med J 2011:13(1):4-6.
[20] Dewi R, Farimatuzzuhroh. Profil pasien sakit kritis yang dirawat di Pediaric Intensive Care Unit Rumah Sakit Cipto Mangunkusumo berdasar sistem skoring Pediatric Logistic organ Dysfunction-2. Sari Pediatri 2019;21(1): 37-43.
[21] World Health Organization. Exclusive breastfeeding for optimal growth, development and health of infants. e-Library of Evidence for Nutrition Actions (eLENA). 2019 [cited August 25 2020]. Available from: https://www.who.int/elena/titles/exclusive_breastfeeding/en/#:~:text=Exclusive%20breastfeeding%20means%20that%20the,of%20vitamins%2C%20minerals%20or%20medicines.
[22] Andhi M. pengertian urban, rural, urban sprawl. 2011 [cited August 25 2020]. Available from: https://malindoandhi.wordpress.com/2011/04/25/pengertian-urban-rural-urban-sprawl-dll/.

[23] Dharaniyadewi D, Lie KC, Suwarto S. Peran procalcitonin sebagai penanda inflamasi sistemik pada sepsis. Jurnal Penyakit Dalam Indonesia 2015;2(2):116-23.
[24] Ciampo ID, Sawamura R, Ciampo LA, Fernandes MI. Acrodermatitis enteropathica: clinical manifestations and pediatric diagnosis. Rev Paul Pediatr 2018;36(2): 238-41.
[25] Sikora SK, Spady M, Prosser C, El-Matary W. Trace elements and vitamins at diagnosis in pediatric-onset inflammatory bowel disease. Clin Pediatr 2015;50(6): 488-92.
[26] Michael K, Chooi JK, Boyd T, Boyd ND. Influence of age and sex on plasma zinc levels in normal and diabetic individuals. Nutr Metabol 1976;20: 135-42.
[27] Wulandari A, Martuti S, Pudjiastuti. Perkembangan diagnosis sepsis pada anak. Sari Pediatri 2017;19(4): 237-44.
[28] Cvijanovich NZ, King JC, Flori HR, Gildengorin G, Wong HR. Zinc homeostasis in pediatric critical illness. Pediatr Crit Care Med 2009;10: 29-34.
[29] Alker W, Haase H. Zinc and sepsis. Nutrients 2018;10: 1-17.
[30] Visalakshy J, Surendran S, Pillai MP, Rajendran A, Sherif AA. Could plasma zinc be a predictor for mortality and severity in sepsis syndrome?. Int J Res Med Sci 2017;5(9): 3929-34.
[31] Linko R, Karlsson S, Pettila V, Okkonen M, Lund V, Ala-Kokko T dkk. Serum zinc in critically ill adult patients with acute respiratory failure. Acta Anaesthesiol Scan 2011;55:615-21.
[32] Negh FF, Soliman DR, Ahmed ES, Rasha AE. Assesment of serum zinc, selemium, and prolactin cncentrations in critically ill children. Pediatr Health Med Therapeu 2016;7 17-23.
[33] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, dkk. The third international consensus definitions foe sepsis and septic shock (sepsis-3). JAMA 2016;315(8): 801-10.
[34] Cander B, Dundar ZD, Gul M, Girisgin S. Prognostic value of serum zinc levels in critically ill patients. J Crit Care 2011;26: 42-46.
[35] Hoeger J, Simon TP, Beeker T, Marx G, Haase H, Schuerholz T. Persistent low serum zinc is associated with reccurent sepsis in critically ill patients-A pilot study. PLOS ONE 2017;5:1-10.