Effect of zinc supplementation in PELOD-2 score and zinc serum level in children with sepsis

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Abstract

***Background*: Sepsis in children still shows a high mortality rate. Nutritional factors are important in the treatment of sepsis. Zinc is one of the key elements that can limit mitochondrial dysfunction due to an imbalance between reactive oxygen species and antioxidants that occur in sepsis. We aim to determine the effect of Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score and zinc serum level before and after zinc supplementation in septic children.**

***Methods*: This is an experimental study with one group pretest-posttest design in patients aged 1 month to 18 years with sepsis treated at the PICU H. Adam Malik General Hospital from March 2018-February 2019. Oral zinc supplementation was given for 5 days. The PELOD-2 score and zinc serum level measurement were performed by using inductively coupled plasma-spectrometry (ICP-MS) on the first and fifth days. Bivariate analysis was performed by paired T test.**

***Results*: A total of 17 patients were analyzed. The paired T test showed significant difference in serum zinc levels before and after supplementation ($p<0.001$) even though the zinc levels were both still below normal values (28.7±11.7 μg/dl and 40.5±18.3 μg/dl, respectively). PELOD-2 score still showed increasing values with significant differences ($p<0.001$) before and after zinc supplementation (7.76±2.4 and 11.7±3.3, respectively).**

***Conclusion*: This was the first report that evaluated effect of zinc supplementation on PELOD-2 score. Zinc supplementation did not decrease PELOD-2 score but could give significant improvement in zinc serum level.**

Key words: Zinc supplementation, PELOD-2, sepsis, children.

Introduction

Sepsis in children still shows a high mortality rate. (1) Various studies suggest that there has been an increase in the number of cases of sepsis in children in two decades, which may be related to the survival of premature and low birth weight babies as well as children with severe chronic disease. Children living in low-income countries also represent populations that are vulnerable to sepsis. (2) Sepsis will cause dysregulation of cytokine activity. Anti-inflammatory response will be induced as a results of this proinflammatory cytokine activity in sepsis. It will cause immune suppression effect that increase body vulnerability of infection and worse outsome. (3) Nutritional factors are important in the management of sepsis. (4) Zinc is one of the key elements that can limit mitochondrial dysfunction due to an imbalance between reactive oxygen species and antioxidants that occur in sepsis. The high severity of sepsis will cause zinc levels in the body to decrease. (5) Several studies have shown the benefits of zinc supplementation in decreasing the incidence of infection and length of stay in hospital, but no study has been done to assess the benefits of oral zinc supplementation in children with sepsis. We conducted this study to determine the effect of zinc supplementation in Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score and zinc serum level in septic children.

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Methods

This study was an experimental study with one group pretest-posttest design that aimed to determine the effect in serum zinc levels and PELOD-2 score before and after zinc supplementation in septic children. The research sample were children aged 1 month to ≤18 years with sepsis who were hospitalized at PICU Haji Adam Malik Hospital, Medan, Sumatera Utara, from March 2018 to February 2019, and obtained by consecutive sampling. All subjects would be asked for parents' approval after an explanation about the condition of the disease. The study was conducted after approval of the Health Ethics Committee from the Faculty of Medicine, Universitas Sumatera Utara and Ethics Committee H. Adam Malik Hospital, Medan. Patients that could not be given enteral feeding were excluded.

Demographic data such as age, gender, weight, height, previous medical history, physical examination, and diagnosis were recorded. Blood samples were taken for complete blood tests, blood cultures, blood gas analysis, kidney function, lactic acid, zinc serum levels. Zinc serum level were done and validated by Mass Spectrometry Laboratory, measured by inductively coupled plasma mass spectrometry (ICP-MS), and the results were recorded in μg/dl unit. Zinc supplementation 20 mg once daily for 5 days. PELOD-2 score calculation and zinc serum level were performed on the first and fifth days of treatment. The patients were followed up during treatment, until they were moved to the ward room, or died.

Univariate analysis was done to determine the distribution of characteristics of research subjects in children with sepsis. Numeric variables were expressed as mean and standard deviation because of normality data distribution and categorical variables were expressed as frequency and percentage. Bivariate analysis was done using T-dependent test. Data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.

Results

During study period, 17 eligible children were included in the study based on inclusion and exclusion criteria. Most subject were malnourished (12 children [70.6%]). The majority of primary infections originating from respiratory system and post surgery for 5 subjects (29.4%). Six subjects (35.3%) gave positive culture results, and 12 subjects (70.6%) died. The baseline characteristic of research samples is presented in **Table 1**.

Significant differences were found in zinc levels before and after zinc supplementation therapy ($p<0.001$). Zinc levels before supplementation had a mean 28.7 μg/dl with standard deviation 11.7, while zinc levels after supplementation had a mean 40.5 μg/dl with standard deviation 18.3. Significant differences were found in PELOD-2 score before and after zinc supplementation therapy ($p<0.001$). The PELOD-2 score before supplementation had a mean 7.76 with a standard deviation 2.4, and increased after supplementation with a mean 11.7 and a standard deviation 3.3. All these results are presented in **Table 2**.

Discussion

Malnutrition was associated with poor outcomes in children with critical illness. In a study conducted by Irving, et al, a secondary analysis of 417 children under 18 years of age with severe sepsis who were treated at the PICU were found that 30% of the children were malnourished and 37% with overnutrition. In this study, it was found only 29.4% children with sepsis were well nourished, while the remaining 70.6% were malnourished. In 2018 Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study found that the highest number of primary infections was in the respiratory tract as much as 40%, and blood flow as much as 19%. (6) This is slightly different from the results of this study which found that there were the same number of respiratory infections and postoperative care in children admitted to the PICU that was 29.4%.

Zinc has an important role in immune function and various biochemical pathways in the body. Zinc deficiency will disrupt the immune system and cause susceptibility to infection. Zinc deficiency also causes changes in the inflammatory response associated with organ damage and higher mortality rates. (7) Study by Wong, et al showed that pediatric patients with septic shock who died had low serum zinc levels of 50-55 μg/dl. (8) Mertens, et al also showed decreased zinc level in septic patients of intensive care units that was 3.1 (range 1.5-5.4 μM), with increased oxidative stress level and elevated markers of inflammation. (9) The results of this study indicated that zinc levels were low in children with sepsis both before (28.7±11.7 μg/dl) and after zinc supplementation (40.5±18.3 μg/dl).

Zinc supplementation was indicated to increase zinc level and improve immune function. Study by Nowak, et al reported that zinc supplementation showed an important role in reducing inflammation, organ damage, and mortality in experimental animals with sepsis during 72 hours of monitoring. (10) Another study by Terrin, et al also showed that zinc supplementation reduced mortality in premature infants with very low birth weight during hospitalization (26.8% vs 41.7%). (11) Similar study conducted by Banupriya, et al on zinc supplementation in neonates also showed lower mortality rates in the zinc supplementation group. (12) Intravenous zinc supplementation conducted in critically ill children by Cvijanovich, et al showed a significant increase in zinc levels from 41.8±16 μg/dl to 93.3±8.75 μg/dl. (13) This study showed that there was a significant levels of zinc serum after zinc supplementation even though it has not reached normal zinc levels.

The PELOD-2 score assessment in this study was carried out in the first 24 hours and after 5 days of zinc supplementation therapy. Study conducted by Cvijanovich, et al showed that low zinc levels were associated with the degree of organ failure being treated in children's intensive care units. (13) Other studies by Negm, et al (14) and Kusuma, et al (15) indicated that decreased zinc level were inversely associated with PELOD scores but this was not found in this study, where there was no visible improvement in lowering PELOD-2 score after zinc supplementation with mortality rate 70.6%.

Some limitations in this study were the research samples that was difficult to obtain because zinc supplementation on the first day could not be given if the subject at admission must be fasted for 24 hours or the subject died before achieving zinc supplementation for 5 days; the subjects were in very little sample size; the study like this has never been done on children in intensive care unit so there was no basic data when starting this research; the administration period for zinc supplementation was shorter than other studies conducted, and various dosages of supplementation among studies can cause diversity on data. At present there is also no intravenous zinc supplementation in Indonesia, so the results that obtained can be different from other studies. Patients who entered the intensive care unit could have variations in the disease course and the broad range of disease severity when the patient was diagnosed with sepsis, resulting in a fairly wide range of data. Further research is needed with a larger sample size, longer intervention duration, and assessment of external factors that can affect zinc levels can be done to obtain additional information about the benefits of zinc supplementation as adjuvant therapy that can be given to children with sepsis who are treated at pediatric intensive care unit.

Table 1. Baseline characteristic of children with sepsis

Indicator	n=17
Gender, n (%) - Boy - Girl	 10 (58.8) 7 (41.2)
Age, n (%) - Under 1 year old - 1-5 years old - 6-10 years old - 11-18 years old	 2 (11.8) 6 (35.3) 2 (11.8) 7 (41.2)
Body weight (kg), median (min-max)	15 (4.6-40)
Body height (cm), median (min-max)	108 (49-160)
Nutritional status, n (%) - Severe malnutrition - Mild-moderate malnutrition - Well nourished	 8 (47.1) 4 (23.5) 5 (29.4)
Primary infection, n (%) - Respiratory disorder - Infection disorder - Neurological disorder - Nephrology disorder - Postoperative management	 5 (29.4) 1 (5.9) 3 (17.6) 3 (17.6) 5 (29.4)
Outcome, n (%) - Move to the ward - Death	 5 (29.4) 12 (70.6)
Blood culture, n (%) - Positive - Negative	 6 (35.3) 11 (64.7)

Table 2. Difference in PELOD-2 score and zinc serum level before and after zinc supplementation

Parameter	Before supplementation	After supplementation	p value
Zinc level (µg/dl), mean±SD	28.7±11.7	40.5±18.3	<0.001*
PELOD-2 score, mean±SD	7.76±2.4	11.7±3.3	<0.001*

Legend: PELOD-2=Pediatric Logistic Organ Dysfunction 2; *T-dependent test

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