

The Effect of Zinc Supplementation on Reducing Dengue-Related Morbidity in Pediatric Patients in Jakarta

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ABSTRACT

Background: Dengue hemorrhagic fever is an endemic disease that causes significant morbidity, particularly in Jakarta. Based on previous studies, zinc has immunomodulatory properties that can function to improve the immune response to infections, including dengue. This study aims to evaluate the effectiveness of zinc supplementation in reducing morbidity and improving clinical conditions in pediatric patients with dengue hemorrhagic fever.

Methods: This study utilized a prospective cohort method with a sample of 200 pediatric patients suffering from dengue hemorrhagic fever. The sample was divided into two groups: the intervention group (given zinc supplementation) and the control group (standard care without zinc supplementation). Laboratory assessments included serum zinc levels, severity of clinical symptoms, and hematological examination results.

Results: The analysis showed a significant increase in serum zinc levels in the group given zinc supplementation, with the mean increasing from $100.34 \pm 27.69 \mu\text{g/dL}$ to $104.28 \pm 28.65 \mu\text{g/dL}$ on day 14 ($p < 0.05$). The number of patients whose clinical symptoms gradually became milder increased from 40% to 55% in the intervention group, whereas in the control group, there was a decrease in the number of patients with gradually milder symptoms, from 40% to 36%.

Conclusion: Zinc supplementation is quite effective in reducing morbidity and improving clinical conditions in pediatric patients with dengue hemorrhagic fever.

INTRODUCTION

Dengue fever is an endemic tropical disease frequently encountered in Jakarta. It is caused by the dengue virus, transmitted by the *Aedes aegypti* mosquito vector. The clinical manifestations of this disease vary widely, ranging from asymptomatic cases to dengue shock syndrome (DSS) [1]. The spread of this disease is exacerbated by Jakarta's dense population and poor environmental hygiene.



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Zinc is a micronutrient that functions as an immunomodulator and holds potential as part of the body's defense mechanism against viral infections. This study aims to evaluate zinc supplementation as an adjunct therapy in the management of pediatric dengue fever cases to reduce morbidity and improve clinical recovery [2]. Zinc plays a vital role in the development and activation of immune cells such as T lymphocytes and natural killer (NK) cells. Research by Rerksuppaphol indicated that zinc supplementation enhances lymphocyte proliferation and cytokine production, such as interferon-gamma, which is crucial for antiviral immune responses [3]. Zinc is also essential for the structural stability of proteins, DNA, and RNA. A study by Costa et al. stated that zinc is involved in more than 300 enzymes and proteins that affect immune function and tissue regeneration [4-7].

Zinc further influences the inflammatory response by suppressing the production of pro-inflammatory cytokines such as IL-6 and TNF-alpha. This helps prevent tissue damage due to excessive inflammation, such as plasma leakage frequently observed in dengue patients. A study by Poojary et al. demonstrated a direct correlation between serum zinc levels and reduced inflammation in dengue patients [8]. Oxidative damage caused by the dengue virus can be mitigated through the action of the enzyme superoxide dismutase (SOD), which protects cells from oxidative stress, with zinc serving as a key component, as reported by Langerman and Ververs [9].

Due to imbalanced diets and low micronutrient intake, zinc deficiency is prevalent in developing countries, including Indonesia. Children with weakened immune systems due to zinc deficiency are more susceptible to viral infections compared to those with healthy immune function [3]. Ajlan et al. reported that zinc supplementation in children with viral infections can accelerate recovery and reduce clinical symptoms [2].

Based on this issue, this study aims to investigate the effect of zinc supplementation on morbidity among pediatric patients with dengue fever in Jakarta. The study measures serum zinc levels in patient blood samples and examines their relationship with the severity of dengue symptoms. In this research, a comparison is made between a group of pediatric patients receiving zinc supplementation and a control group receiving standard care without zinc. Serum zinc levels are measured, and clinical symptom severity is observed at various time points during the recovery period.

METHODS

Study Participants

This study employed a prospective cohort design targeting pediatric aged 1–11 years who were diagnosed with dengue fever based on WHO clinical and laboratory criteria. Patients were recruited from three healthcare facilities in Jakarta between January and December 2023. The

sample size was calculated using the mean difference formula. Based on the calculation, the required sample size was 63 children per group. For two groups, the total sample was 126 children. In this study, a sample size of 200 pediatric patients was determined, meaning that a redundancy of 37% was included to anticipate potential dropouts from the required total sample. Inclusion criteria were as follows: (a) children aged 1 to 11 years, (b) diagnosed with dengue fever based on WHO clinical and laboratory criteria, and (c) obtained written informed consent from parents or guardians to participate in the study. Exclusion criteria included: (a) children with severe comorbidities such as kidney failure or other chronic diseases, (b) having received zinc supplementation in the last 30 days, and (c) allergy to zinc. Stratified random sampling was used to minimize bias and ensure the validity of study results.

Measurement Procedure

Venous blood samples were collected from the antecubital vein using sterile needles and vacutainer tubes. Observations were conducted at three time points: baseline (Day 0), Day 7, and Day 14. Serum zinc levels, platelet counts, hematocrit values, and clinical symptom assessments based on WHO dengue criteria were recorded. Demographic and clinical data were collected from the patients' medical records. Serum zinc levels were measured using an Atomic Absorption Spectrophotometer (AAS). The severity of symptoms was classified based on WHO categories. Platelet count and hematocrit levels were also measured.

The severity of dengue symptoms was assessed using the WHO criteria, with the following scoring system [2] :

1. Dengue without warning signs: fever (score 1), mild muscle/joint pain: (score 1), skin rash (score 1). Total score: 3 or less.
2. Dengue with warning signs: severe abdominal pain (score 2), persistent vomiting (score 2), mucosal bleeding (score 2), liver enlargement >2 cm (score 2). Total score: 4-6.
3. Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS): hypovolemic shock (score 3), severe plasma leakage (score 3), severe bleeding (score 3), severe organ involvement (liver, heart, nervous system) (score 3). Total score: 7 or more.

Management and Zinc Supplementation

Both the intervention and control groups received standard care based on the national protocol for dengue fever. Standard management included: intravenous (IV) fluid therapy to prevent dehydration and hypovolemic shock, antipyretics to reduce fever and manage myalgia, antiemetics for nausea and vomiting as needed, H2-receptor blockers or proton pump inhibitors (PPIs) for gastrointestinal symptoms, and antibiotics only when secondary infections were suspected. The intervention group received zinc supplementation in the form of zinc sulfate at a dose of 20 mg per day, administered orally for 14 days. Zinc supplementation was given with meals to improve absorption and reduce the risk of gastrointestinal side effects.

Adverse Event Assessment

Adverse events, ranging from mild (e.g., nausea or mild abdominal discomfort) to moderate/severe, were assessed through direct interviews with the children's parents/guardians and clinical observation by the medical team. Adverse events were recorded daily throughout the treatment period.

Data Analysis

Statistical analysis in this study was conducted using SPSS version 25, including: descriptive statistics to describe baseline characteristics, ANOVA to compare changes in serum zinc levels at various time points, Pearson correlation test to evaluate the relationship between serum zinc levels and platelet count as well as hematocrit values, logistic regression to assess the association between serum zinc levels and the severity of dengue symptoms. Paired t-test to assess changes within the same group at two different time points, and independent t-test to compare between groups at the same time point.

RESULTS

The study included 200 pediatric participants aged 1–11 years, with a mean age of 6.6 years (± 3.2 SD) and a median age of 7 years, indicating a predominantly young cohort. Sex distribution was nearly equal (51% male, 49% female). Participants were equally allocated to the control group (n=100, 50%) and intervention group (n=100, 50%), ensuring balanced group comparisons. The young age range suggests findings are most applicable to early childhood, while the balanced sex distribution and equal group allocation support the internal validity of comparisons between the control and intervention arms (Table 1).

Table 1. Characteristics of Study Subjects

Characteristic	n	%	Mean $\pm$ SD	Median (Min–Max)
Age (years)	200	100	6,6 $\pm$ 3,2	7 (1–11)
Sex				
Male	102	51		
Female	98	49		
Group				
Control	100	50		
Intervention	100	50		

The mean serum zinc levels of pediatric dengue patients in both the control and intervention groups were measured at three time points: baseline, day 7, and day 14. The data show changes in zinc levels and symptom severity over time. The mean serum zinc levels in the intervention group showed a more consistent increase compared to the control group (Table 2).

The severity of dengue symptoms also demonstrated more improvement in the intervention group. The graph presents data for two groups: the control group, consisting of

patients who received standard care without zinc supplementation, is represented by the blue line, while the intervention group, consisting of patients who received zinc supplementation in addition to standard care, is represented by the red line. The graph illustrates the changes in the percentage of patients in each category of dengue symptom severity at three time points: baseline (at diagnosis), day 7, and day 14. The results show that in the intervention group (which received zinc), there was increase the number of patients classified as having "dengue without warning signs" from baseline to day 14. In contrast, no such increase was observed in the control group. These findings indicate that zinc supplementation may offer benefits in reducing morbidity among pediatric dengue patients in Jakarta (Figure 1).

Table 2. Mean Serum Zinc Levels During Different Phases of Treatment

Treatment Phase	Group	n	Mean $\pm$ SD ($\mu\text{g/dL}$)	Median (Min–Max)
Baseline	Control	100	104,57 $\pm$ 28,30	102,76 (50,02–149,92)
	Intervention	100	100,34 $\pm$ 27,69	99,25 (50,12–148,68)
Day 7	Control	100	105,46 $\pm$ 27,20	105,47 (51,09–149,99)
	Intervention	100	103,74 $\pm$ 28,34	104,24 (50,01–148,93)
Day14	Control	100	106,52 $\pm$ 28,48	105,71 (50,29–149,99)
	Intervention	100	104,28 $\pm$ 28,65	103,95 (50,13–148,90)

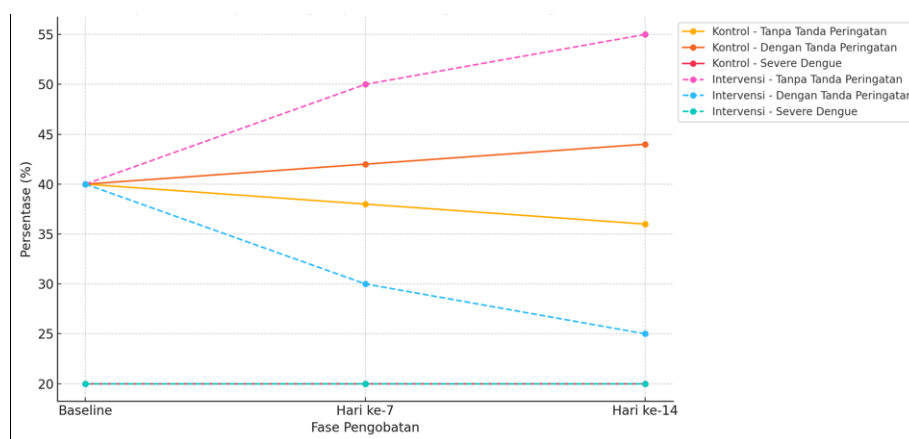


Figure 1. Severity of Dengue Symptoms at Different Phases of Treatment

The graph illustrates increase of serum zinc levels between the intervention and control groups over time. The interaction between time and treatment, indicating that changes in serum zinc levels differed between the two groups at different time points (Figure 2).

The logistic regression analysis showed an odds ratio (OR) of 0.82, indicating that each one-unit increase in serum zinc level was associated with an 18% decrease in the odds of experiencing dengue with warning signs or severe dengue (since $1 - 0.82 = 0.18$ or 18%). The 95% confidence interval (CI) was 0.72–0.94, suggesting that the researchers are 95% confident that the true OR lies between 0.72 and 0.94. Since this interval does not include 1, the relationship between zinc

levels and symptom severity is considered statistically significant. A p-value of 0.001 further confirms the significance of this association (Table 3).

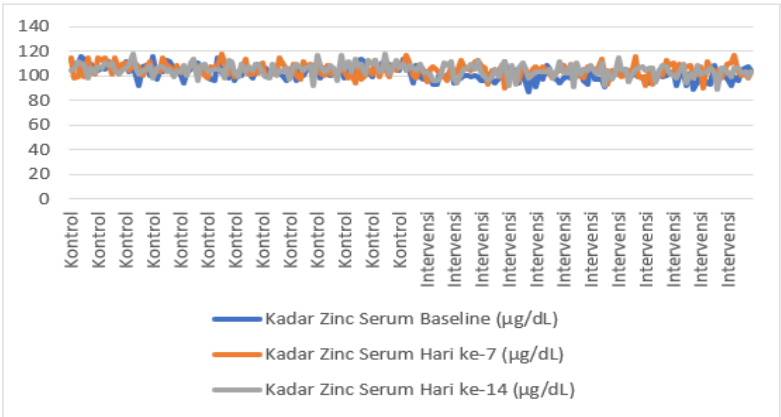


Figure 2. Serum Zinc Levels in Pediatric Dengue Patients at Baseline, Day 7, and Day 14

Table 3. Logistic Regression Results

Variable	Coefficient (β)	Odds Ratio (OR)	95% CI (Lower)	95% CI (Upper)	p-value
Intercept	1.5				0.001
Serum Zinc Level	-0.2	0.82	0.72	0.94	0.001

Table 4 shows a more consistent and significant increase in platelet count in the intervention group compared to the control group ($p < 0.05$). The hematocrit levels in the intervention group were more stable compared to the control group, indicating that the group receiving zinc supplementation responded better to plasma leakage. A significant positive correlation was found between serum zinc levels and platelet count ($r = 0.362$, $p = 0.001$), as well as a negative correlation with hematocrit levels ($r = -0.298$, $p = 0.003$).

Table 4. Mean Platelet Count and Hematocrit Values

Time	Group	Platelet Count ($\times 10^9/L$)	P value	Hematocrit Value (%)	P value
Baseline	Control	109.2 ± 37.8	0.000*	39.5 ± 4.0	0.000*
	Intervention	110.5 ± 35.0		40.0 ± 3.8	
Day 7	Control	112.0 ± 36.0	0.000*	41.5 ± 4.5	0.000*
	Intervention	115.0 ± 35.5		40.8 ± 4.2	
Day 14	Control	115.5 ± 34.5	0.000*	42.0 ± 4.0	0.000*
	Intervention	120.0 ± 32.5		40.5 ± 3.9	

*Paired T-test.

Serum zinc levels and platelet count ($r = 0.362$, $p = 0.001$), serum zinc levels and hematocrit levels ($r = -0.298$, $p = 0.003$).

Analysis of the Relationship Between Serum Zinc Levels and Platelet Count

To evaluate the relationship between increased serum zinc levels and platelet count, a Pearson correlation analysis was conducted. The analysis revealed a significant positive correlation between increased serum zinc levels and platelet count in the intervention group on day 14 ($r = 0.362$, $p = 0.001$). This indicates that higher serum zinc levels are associated with an increase in platelet count.

Analysis of the Relationship Between Serum Zinc Levels and Hematocrit Levels

Pearson correlation analysis was also performed to evaluate the relationship between serum zinc levels and hematocrit levels. The results showed a significant negative correlation between serum zinc levels and hematocrit levels in the intervention group on day 14 ($r = -0.298$, $p = 0.003$). This suggests that increased serum zinc levels are associated with more stable or lower hematocrit values, indicating better control of vascular permeability.

Assessment of Side Effects

Zinc supplementation was well tolerated by pediatric patients, with no significant side effects observed. The frequency of mild side effects, such as nausea and gastrointestinal discomfort, was 5% in the intervention group and was considered low and acceptable in the context of the benefits gained from zinc supplementation. The absence of serious adverse effects supports the safety of zinc use at the dosage applied in this study (20 mg per day for 14 days).

DISCUSSION

This study demonstrated that zinc supplementation significantly increased serum zinc levels in the intervention group compared to the control group. This finding aligns with the study by Rerksupphol et al., which stated that children with zinc deficiency are more vulnerable to worsening symptoms of dengue. Research by Poojary et al. also reported a positive correlation between higher serum zinc levels and a reduction in dengue symptom severity [8].

A greater proportion of patients in the intervention group showed clinical improvement, increasing from 40% to 55%, compared to a decrease from 40% to 36% in the control group. These findings are consistent with research by Ajlan et al. which emphasized the importance of clinical assessment based on WHO classification to identify changes in dengue severity [2]. Zinc's immunomodulatory effects play a key role in enhancing the immune response to viral infections, as described by Costa et al., supporting the finding that zinc strengthens the body's defense mechanisms against the progression of severe symptoms [4].

This study showed a significant increase in platelet count in the intervention group ($r = 0.362$, $p = 0.001$). This is in line with the findings of Made et al, who noted that a drop in platelet count is a critical indicator of dengue severity [1]. A significant negative correlation was also found between serum zinc levels and hematocrit values ($r = -0.298$, $p = 0.003$), indicating better

hematocrit stability in the group receiving zinc supplementation. This result is supported by Idrus et al. (2023), who reported that hematocrit stability is a key indicator in preventing complications such as plasma leakage [6].

The frequency of mild side effects such as nausea in the intervention group was only 5%, with no serious adverse events reported. Langerman and Ververs stated in their study that micronutrient supplementation, including zinc, carries minimal risk of side effects when used as an adjunct therapy [9]. The antioxidant properties of zinc help reduce oxidative damage caused by dengue virus infection, as explained by Panwar et al by strengthening endothelial protection in the vasculature and preventing plasma leakage [12].

Zinc supplementation was well tolerated by pediatric patients, with no significant side effects observed. These findings are consistent with research by Rerksuppaphol, which also reported that zinc supplementation was well tolerated with no significant side effects in children with dengue virus infection. Other studies in the context of childhood diarrhea have also shown that zinc supplementation is safe and has minimal side effects, especially at the recommended dosage [10-12].

CONCLUSION

The results of this study are consistent with previous research showing that zinc has immunomodulatory effects, supports hematologic function, and improves the inflammatory response in patients with dengue. In the future, zinc may serve as a safe and effective adjunct therapy in the management of dengue fever.

DECLARATIONS

Ethics approval

Ethical approval was obtained from the SMC Jakarta Ethics Committee, approval number XI/ESMC/VII/2023. All procedures followed applicable ethical research guidelines. Parents or guardians of each research subject received detailed explanations regarding the objectives, procedures, benefits, and risks before providing written informed consent.

Conflict of interest.

The authors declare no conflict of interest.

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