ORIGINAL ARTICLE

The Effect of Vitamin D3 Supplementation on Interleukin-6 and PRESS Score in Children with Pneumonia and Vitamin D Deficiency

Retno Asih Setyoningrum[1,2*], Wigit Kristianto[1,2], Arda Pratama Putra Chafid[1,2], Rika Hapsari[1,2], Irmi Syafa'ah[3,4]

[1]Department of Child Health, Dr. Soetomo General Academic Hopital, Surabaya, Indonesia.
[2]Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[3]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[4]Ph.D. Program in Graduate Institute of Biomedical Science, College of Medicine, China Medical University, Taichung, Taiwan.

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ABSTRACT

Introduction: Pneumonia is a significant health issue in children under 5 years old. Vitamin D may help to reduce childhood mortality, morbidity, and interleukin-6 (IL-6) levels in children with pneumonia, but the evidence is still limited and controversial. This study aimed to evaluate the effect of vitamin D3 supplementation on IL-6 levels and clinical manifestations in children with pneumonia and vitamin D inadequacy.
Methods: This was a randomized, placebo-controlled, and double-blinded trial study. Twenty-eight children diagnosed with pneumonia and vitamin D deficiency were enrolled and divided into a supplementation (n=15) or placebo group (n=13). Children were given a single dose (100,000 international units/IU) of vitamin D3 or placebo on the first day of hospitalization. Clinical manifestations were assessed by the Pediatric Respiratory Severity Score (PRESS).
Results: The level of 25-hydroxyvitamin D (25-OH D3), IL-6, and PRESS score at baseline showed no significant difference between groups. Seven days post-supplementation, only the PRESS score showed a significant difference between groups (p=0.025). Analysis of the vitamin D3 group showed a significantly increased 25-OH D3 level and a reduced PRESS score (p=0.039 and p=0.02, respectively).
Conclusion: A single high dose of vitamin D3 supplementation in children with pneumonia and inadequate vitamin D levels helps elevate 25-OH D3 levels and reduce clinical manifestations, as indicated by the PRESS score.

INTRODUCTION

Pneumonia remains a major global health concern, particularly for children under five years of age. Despite significant progress in reducing mortality, pneumonia was still the leading cause of death in this age group in 2019, accounting for approximately 0.74 million deaths (0.62–0.84 million; 13.9% [12.0–15.1]).[1] As the burden of disease persists, there is a need for continued efforts in management and prevention. Antibiotics have long been the cornerstone of pneumonia treatment, while vaccination campaigns have played an important role in preventing pneumonia incidence.[2] Unfortunately, growing antibiotic resistance poses a significant challenge. A previous study highlighted that resistance spans nearly all classes of antibiotics commonly used to treat pneumonia-causing pathogens, raising concerns about the long-term efficacy of these treatments.[3]

Given these limitations, studies exploring adjunctive therapies have become important. One promising option is vitamin D, which may help reduce childhood mortality associated with pneumonia. Vitamin D functions as an immunomodulatory agent, with the activation of vitamin D receptors (VDR) playing a critical role in immune regulation. By modulating immune cell activity, VDR activation decreases pro-

*Corresponding author: retno-a-s@fk.unair.ac.id

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inflammatory cytokines and increases anti-inflammatory cytokines, potentially enhancing the body's ability to combat infections.[4] Considering the persistently high mortality rates, exploration of the efficacy of vitamin D supplementation is urgently needed. Observational studies consistently show an inverse relationship between vitamin D levels and pneumonia severity, underscoring its potential role in disease management.[5–8]

Despite this promising evidence, randomized clinical trials on the effect of vitamin D3 supplementation as an adjunct therapy in children with pneumonia remain limited. Some studies found no significant differences in key clinical outcomes, such as the time to resolution of severe pneumonia or length of hospital stay, between children receiving 100,000 international units (IU) of oral vitamin D3 and those given a placebo.[9–12] However, these studies often included children regardless of their baseline vitamin D status, potentially diluting the observed effects. In contrast, another study indicated that vitamin D3 injection (100,000 IU) improved clinical outcomes, including reduced time to recovery, decreased Pediatric Sequential Organ Failure Assessment (pSOFA) scores, and enhanced partial pressure of arterial oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratios, specifically in children with pneumonia and vitamin D inadequacy.[13] These findings suggest that the benefits of vitamin D3 supplementation may be most pronounced in subgroups with pre-existing vitamin D deficiency or inadequacy. This underscores the necessity for further research to identify populations that would benefit most from such interventions.

Interleukin-6 (IL-6), a cytokine with a well-established role in inflammation, is recognized as a key biomarker of pneumonia severity in both pediatric and adult populations.[14–16] Previous observational studies reported that children with pneumonia and vitamin D deficiency had higher IL-6 levels than children with pneumonia and normal vitamin D status.[17,18] This association highlights the potential of vitamin D to influence pneumonia outcomes through its effects on IL-6. While studies investigating the impact of vitamin D3 supplementation on IL-6 levels in children with pneumonia are scarce, findings from adult populations are encouraging. For instance, a study involving adults with ventilator-associated pneumonia (VAP) and vitamin D deficiency (<30 ng/mL) reported significant reductions in IL-6 levels following intramuscular supplementation of 300,000 IU vitamin D3 over seven days.[19]

Building on these insights, this study aimed to evaluate the effect of a single 100,000 IU dose of vitamin D3 supplementation on IL-6 levels and clinical manifestations in children diagnosed with pneumonia and vitamin D inadequacy. Clinical outcomes were assessed using the Pediatric Respiratory Severity Score (PRESS), a reliable tool for measuring respiratory distress in children. By focusing on a population with documented vitamin D inadequacy, this study sought to address the gaps in existing research and provide evidence to guide the use of vitamin D as a targeted adjunct therapy in pediatric pneumonia management. These findings could initiate the integrated approaches of managing pneumonia in children, especially by combining traditional treatments to improve outcomes and reduce morbidity.

METHODS

Research Design

This was a randomized controlled trial study. Placebo was used as a control, while 100,000 IU of vitamin D was the intervention. This double-blinded trial was conducted at Dr. Soetomo General Academic Hospital, Surabaya. Forty-five children aged 1–60 months admitted to the emergency department and diagnosed clinically as having pneumonia were screened for vitamin D inadequacy status. Children with a history of vitamin D3 supplementation four weeks prior to admission, history of antibiotic use >3 days before admission, congenital heart disease, renal injury, and normal vitamin D status (>30 ng/mL) were excluded. Randomization was generated using a computer to allocate subjects into two groups.

Data Collection

Baseline data, including gender, age, weight, and height, were collected from all participants. Presenting symptoms and signs of pneumonia were evaluated and transformed into PRESS on the first day of hospitalization. The PRESS comprised five parameters: the presence of tachypnea, wheezing, chest retraction, O_2 saturation levels, and feeding difficulties. Each parameter was assigned a binary score of either 0 (absent) or 1 (present), based on the clinical findings observed during examination.[20]

Blood samples for laboratory measurements were collected from participants on the first and seventh day of hospitalization. These samples were processed and analyzed under standardized conditions. The serum 25-hydroxyvitamin D (25-OH D3) levels were measured using an enzyme-linked immunosorbent assay (ELISA) CAN-VD-510 kit (DBC Diagnostic Biochem Canada Inc.) Interleukin-6 levels were measured by IL-6 ELISA Kit 96T (E090Hu).

Intervention

The vitamin D3 group received a single dose of 100,000 IU of vitamin D3 via oral or nasogastric administration on the first day of hospitalization, while the placebo group received a placebo. Both vitamin D3 and placebo preparations were identical in appearance, odor, volume, and taste, ensuring blinding. These preparations were carefully formulated by pharmacy staff and distributed under strict blinding protocols to maintain study integrity. Neither the researchers nor the subjects were aware of group assignments. All participants in both groups received standard medical care for pediatric pneumonia according to the clinical guidelines practiced at Dr. Soetomo General Academic Hospital, Surabaya.

Statistical Analysis

Data were presented as frequencies for categorical variables and median (interquartile range/IQR) for continuous variables. For categorical variables, comparisons were conducted using the chi-square test or Fisher's exact test. For continuous data, the Mann-Whitney U test was used for independent data comparison, while the Wilcoxon signed-rank test was used for paired data comparison. Statistical significance was considered when p-values were less than 0.05.

Ethical Clearance

Ethical clearance for this study was obtained from the Ethics Committee of Health Research of Dr. Soetomo General Academic Hospital, Surabaya (No.0379/KEPK/III/2022). The study adhered to the ethical principles outlined in the Helsinki Declaration of 1975, including its later amendments. Written informed consent was voluntarily provided by the parents or guardians of all participants before enrollment. Participants were assured of the confidentiality of their data and their right to withdraw from the study at any time without any consequences to their standard care.

RESULTS

Baseline Characteristics of Subjects

Of the 28 children diagnosed with pneumonia and vitamin D inadequacy (<30 ng/dL), 15 were assigned to the vitamin D3 group, while 13 were allocated to the placebo group (Table 1). A comparative analysis of baseline characteristics showed no significant differences between groups in gender distribution (46.7% girls in the vitamin D3 group vs. 30.8% in the placebo group), age (median 29 months vs. 6 months), weight (median 9 kg vs. 6 kg), height (median 88 cm vs. 67 cm), or nutritional status. The length of stay was also similar between the groups, with both showing a median of nine (9) days.

Table 1. Baseline characteristics of study participants

Variable	Placebo (n=13)	Supplementation (n=15)	p-value
Gender [n (%)]			
Girl	4 (30.8)	7 (46.7)	0.390[c]
Boy	9 (69.2)	8 (53.3)	
Age (months)	6 (3-24)	29 (4-55)	0.118
Weight (kg)	6 (4-9.45)	9 (6-11)	0.118
Height (cm)	67 (52-86)	88 (62-94)	0.363
Nutritional status			
Severely wasted	4 (30.8)	4 (26.7)	
Wasted	1 (7.7)	2 (13.3)	1.000[f]
Normal	8 (61.5)	8 (53.3)	
Overweight	0 (0)	1 (6.7)	
Length of stay (day)	9 (8.5-11.5)	9 (7-10)	0.339

[c]Chi-square test; [f]Fisher's exact test

Comparison of Variables between Groups

Baseline measurements of 25-OH D3, IL-6, and PRESS were comparable between the two groups. The median 25-OH D3 levels were 22.77 ng/dL (IQR: 17.78–26.92) in the vitamin D3 group and 23.25 ng/dL (IQR: 18.55–25.80) in the placebo group (p=0.892). Median IL-6 levels were 51.96 pg/mL (IQR: 20.26–169.36) in the vitamin D3 group and 50.58 pg/mL (IQR: 33.84–99.29) in the placebo group (p=0.964). The PRESS score median was 3 (IQR: 3–4) in the vitamin D3 group and 3 (IQR: 2–4) in the placebo group (p=1.000).

On the seventh day post-supplementation, the PRESS score was significantly (p=0.025) lower in the vitamin D3 group, with a median of 2 (IQR: 1–2), compared to the placebo group with a median of 2 (IQR: 2–3). The 25-OH D3 level increased to a median of 38.55 ng/dL (IQR: 22.71–48.21) in the vitamin D3 group, while the placebo group remained at 23.41 ng/dL (IQR: 17.95–29.56; p=0.185). Interleukin-6 levels showed a median increase to 55.81 pg/mL (IQR: 32.68–109.82) in the vitamin D3 group, while the placebo group showed a median decrease to 37.52 pg/mL (IQR: 20.26–79.07; p=0.294) (Table 2).

Table 2. Comparison of variables between groups

Variable	Placebo (n=13)	Supplementation (n=15)	p-value
1st day of hospitalization			
25-hydroxyvitamin D (25-OH D3)	23.25 (18.55-25.8)	22.77 (17.78-26.92)	0.892
Interleukin-6	50.58 (33.84-99.29)	51.96 (20.26-169.36)	0.964
Pediatric Respiratory Severity Score (PRESS)	3 (2-4)	3 (3-4)	1.000
7 days after supplementation			
25-OH D3	23.41 (17.95-29.56)	38.55 (22.71-48.21)	0.185
Interleukin-6	37.52 (20.26-79.07)	55.81 (32.68-109.82)	0.294
PRESS	2 (2-3)	2 (1-2)	0.025*

*Significant value (p-value <0.05)

An analysis of the vitamin D3 group showed that supplementation with a dose of 100,000 IU vitamin D3 significantly increased the level of 25-OH D3 from a median of 22.77 ng/dL (IQR: 17.78–26.92) to 38.55 ng/dL (IQR: 22.71–48.21; p = 0.015). This increase was accompanied by a significant reduction in the PRESS score from a median of 3 (IQR: 3–4) to 2 (IQR: 1–2; p=0.002). The IL-6 levels showed a slight increase from a median of 51.96 pg/mL (IQR: 20.26–169.36) to 55.81 pg/mL (IQR: 32.68–109.82; p=0.363) (Table 3).

Table 3. Comparison of variables in the vitamin D3 group

Variable	Pre-Supplementation	Post-Supplementation	p
25-hydroxyvitamin D	22.77 (17.78-26.92)	38.55 (22.71-48.21)	0.015*
Interleukin-6	51.96 (20.26-169.36)	55.81 (32.68-109.82)	0.363
Pediatric Respiratory Severity Score	3 (3-4)	2 (1-2)	0.002*

*Significant value (p-value <0.05)

DISCUSSION

This study was designed to evaluate the effect of oral vitamin D3 (100,000 IU) on IL-6 levels and clinical manifestations, represented by the PRESS score, in children with pneumonia and vitamin D inadequacy. Unlike most previous studies on vitamin D3 supplementation in children with pneumonia, this study specifically focused on a population with confirmed vitamin D inadequacy, encompassing both deficiency and insufficiency. This approach makes it possible to investigate the potential benefits of supplementation in a subgroup that might derive the greatest advantage.

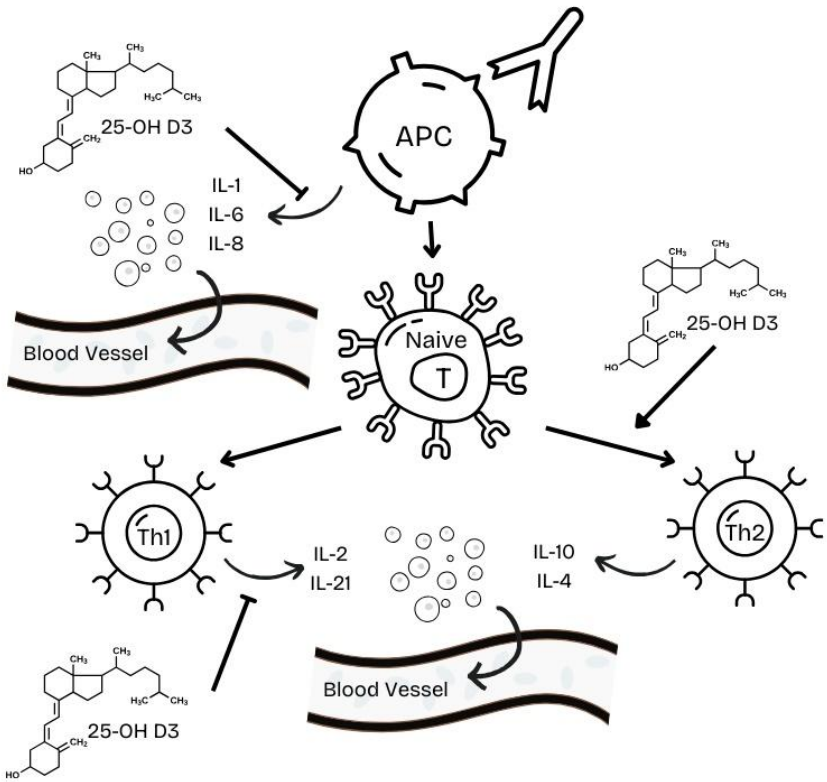

Figure 1. Role of vitamin D3 in modulating immune response

Vitamin D3 plays a crucial role in immune regulation, particularly in balancing pro-inflammatory and anti-inflammatory cytokines (Figure 1). Adequate levels of vitamin D3 promote the differentiation of naïve T cells into T helper (Th) 2 cells, leading to increased production of anti-inflammatory cytokines such as IL-10, IL-5, and IL-4. Conversely, vitamin D3 deficiency may shift the immune response toward a Th1 phenotype, characterized by increased production of pro-inflammatory cytokines such as IL-1, IL-6, and IL-8.[21] Elevated IL-6 levels increase vascular permeability and neutrophil infiltration, leading to prolonged and more severe pulmonary inflammation in children with pneumonia.[14]

This study showed that on the seventh day post-supplementation, the 25-OH D3 levels were significantly increased in the vitamin D3 group. These results align with previous studies that demonstrated significant differences in 25-OH D3 levels after one or two weeks of supplementation with 100,000 IU of vitamin D3 compared to a placebo.[13,22] However, children in the vitamin D3 group experienced a significantly increased 25-OH D3 level after seven days. This result was in accordance with a previous study, which showed a significant increase in 25-OH D3 after three days of vitamin D3 supplementation orally (100,000 IU).[23]

Previous observational studies reported that children with pneumonia and inadequate vitamin D had higher IL-6 levels.[17,18] Children aged 2 months to 3 years old showed a weak correlation between 25-OH D3 and IL-6 level (rs=0,133, p=0.007).[22] Supplementation of intramuscular 300,000 IU vitamin D3 in adults with VAP and vitamin D inadequacy (<30 ng/mL) significantly decreased the IL-6 level after seven days.[19] A single oral dose of 150,000 IU of vitamin D3 could also reduce the IL-6 level after eight days in children with sepsis and vitamin D deficiency.[23] Different results may be caused by a higher dose (150,000 IU) and a different diagnosis (sepsis) in the previous study.[23]

This study demonstrated that the PRESS score after seven days of supplementation was significantly lower in children who received vitamin D3 supplementation. This finding is consistent with a previous study that administered an injection of 100,000 IU of vitamin D3 to children with pneumonia and vitamin D inadequacy.[13] This study reported a reduction in recovery time and pSOFA scores, along with an improvement in PaO_2/FiO_2. To the best of the authors' knowledge, this is the first study to utilize the PRESS score to evaluate clinical manifestations in children related to vitamin D3 supplementation. Originally developed in Japan, the PRESS score was designed to assess the severity of respiratory tract infections.[24] It is a simple severity scoring system that is applicable in healthcare facilities with limited resources or at the community level.[24,25]

Vitamin D supplementation can decrease the clinical manifestations of children with pneumonia and vitamin D inadequacy. A systematic review of seven studies concluded that vitamin D3 supplementation has a minimal effect on the time to resolution.[26] This likely occurred because the effect of vitamin D supplementation on time to symptom resolution might have been confined to children with vitamin D deficiency, although the evidence is still limited.[27] However, vitamin D3 supplementation in children reported no significant effect on the reduction of duration of hospital stay.[28]

Regarding clinical outcomes such as the length of stay (LOS), this study was consistent with earlier studies. A previous study indicated that oral supplementation with 100,000 IU vitamin D3 did not significantly shorten LOS in children diagnosed with pneumonia and vitamin D inadequacy compared to a placebo.[28] Similarly, vitamin D3 supplementation in children with pneumonia without specification of their vitamin D status also failed to show a notable reduction in LOS.[29] These findings suggest that while vitamin D3 supplementation may improve biochemical markers and certain clinical parameters, its impact on hospitalization duration remains inconclusive.

This study only evaluated vitamin D supplementation in children with confirmed deficiencies. Consequently, further research is necessary to validate its use in children without vitamin D deficiency. Notably, high-dose vitamin D supplementation has demonstrated a favorable safety profile. A previous study has shown that even high doses of vitamin D, up to 600,000 IU, are well-tolerated in children aged 0–6 years old, with no serious adverse effects reported in terms of clinical manifestations or biochemical markers such as calcium levels.[29] Furthermore, vitamin D has shown a positive impact on reducing the severity of pulmonary tuberculosis and the frequency of childhood asthma exacerbations.[6,30,31] Vitamin D deficiency has also been associated with future health problems, such as cardiometabolic disorders, acute coronary syndrome, abdominal obesity, type 2 diabetes, hypertension, and malignancies.[32–34]

CONCLUSION

This study concluded that supplementation with a single dose of oral vitamin D3 (100,000 IU) in children diagnosed with pneumonia and vitamin D inadequacy effectively improved 25-OH D3 levels and reduced clinical manifestations, as indicated by a significant

decrease in the PRESS score after seven days of supplementation. These findings highlight the potential benefits of vitamin D3 in managing pneumonia in children with inadequate vitamin D levels. However, further research is warranted to address existing limitations and variability in study protocols, including differences in supplementation dose, frequency, and duration, which continue to yield inconsistent results across studies. Future studies should also explore larger sample sizes, longer follow-up periods, and the potential impact of differentiating pneumonia etiologies to provide more definitive conclusions.

LIMITATIONS OF THE STUDY

The most notable limitation is the relatively small sample size, which may have restricted the statistical power of the findings. As this is a preliminary study, larger trials are necessary to validate these results and provide more robust conclusions. Additionally, this study did not differentiate the etiology of pneumonia, which could influence cytokine profiles and the clinical response to vitamin D supplementation. Viral and bacterial pneumonia may elicit distinct immune responses, and this differentiation could provide more nuanced insights into the role of vitamin D.

Another limitation is the cross-sectional design, which prevented this study from capturing the seasonal variations in 25-OH D3 levels or the potential seasonal patterns in pneumonia etiology. Vitamin D levels are known to fluctuate with sun exposure, and this variation could influence both baseline levels and the response to supplementation. Furthermore, this study did not investigate the potential long-term effects of vitamin D supplementation, leaving questions about its sustained impact on immune function and overall health unanswered.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conception, design, supervision, funding: RAS. Design: RAS, WK. Data collection and/or processing: WK. Materials, analysis and/or interpretation, literature review, writing: RAS, WK, APPC, RH, IS. Critical review: AAPC, RH, IS.

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