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Original article

# Randomized trial of high-dose vitamin D3 supplementation on interleukin-8 modulation in pediatric pneumonia

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**Abstract.** *Background and aim:* The immunomodulatory role of vitamin D in respiratory infections has been suggested, but its impact on inflammatory cytokines like interleukin-8 (IL-8) in pediatric pneumonia remains unclear. This study evaluates the impact of vitamin D3 supplementation on serum 25-hydroxyvitamin D3 [25(OH)D3] and IL-8 levels in children diagnosed with pneumonia. *Methods:* This study was double-blind randomized controlled trial, 45 children with pneumonia were assigned to intervention group (single dose vitamin D3 100,000 IU) (n=23) or placebo group (n=22). Serum 25(OH)D3 and IL-8 levels measured pre- and post-intervention were compared. *Results:* Vitamin D3 supplementation significantly increased of 25(OH) D3 levels 26.9 (Interquartile Range [IQR] 19.2-31.1) ng/mL to 35.7 (IQR 22.7-48.2) ng/mL (p=0.048). But no significant result was found in placebo group (27.3 [IQR 21.9-33.1] to 24.8 [IQR 21.6-36.2], p=0.884). However, there was no significant difference in IL-8 levels between the supplementation and placebo groups post-intervention (p=0.666). *Conclusions:* While high-dose vitamin D3 supplementation effectively improved vitamin D levels in children with pneumonia, it did not significantly reduce IL-8 levels. These findings also highlight the importance adequate vitamin D levels but need for further research to explore its role in pediatric pneumonia therapy. (www.actabiomedica.it)

**Key words:** pediatric pneumonia, 25-hydroxyvitamin D3, interleukin-8, randomized controlled trial, vitamin D supplementation, child health, immune response

## Introduction

Pneumonia continues to be one of the main causes of morbidity and death in children younger than five. In 2019, pneumonia accounted for approximately 736,700 deaths, representing 13.9% from all cause of death among children under five years old (1). Effective management strategies have significantly contributed to reducing pneumonia-related mortality (2). Adjunct therapies, such as corticosteroid and zinc, have been reported to reduce the severity, reduce the risk of treatment failure, and promote faster recovery (3-6). As a result, many studies have explored the effect of adjunct therapies on improving outcomes in pediatric pneumonia (7, 8). Vitamin D has recognized as a potential therapeutic agent due to its immunomodulatory properties (9). It enhances the host immune response by modulating the expression of inflammatory cytokines (10). Observational studies have shown that the low levels of vitamin D are associated with more severe disease and complications (11, 12). Studies exploring the impact of vitamin D supplementation on pediatric pneumonia have shown inconsistent results (13-16). These inconsistencies may be attributed to variations in the disease severity and the dosages of vitamin D used. Interleukin-8 (IL-8) is a chemokine that plays a key role in neutrophil recruitment and activation. Elevated IL-8 levels have been linked to greater disease severity and

poorer clinical outcomes in pediatric pneumonia (17). Most studies to date have reported the effects of vitamin D on common inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6) (18, 19). However, there is limited evidence on the impact of vitamin D supplementation on interleukin-8 (IL-8). This study aims to investigate the effect of vitamin D supplementation on serum 25-hydroxyvitamin D3 [25(OH)D3] and IL-8 levels in children with pneumonia. By focusing on IL-8, this study seeks for new insight into the immunomodulatory effects of vitamin D and its potential role as an adjunct therapy in managing pediatric pneumonia.

## Methods

*Study design and setting*

This double-blind randomized controlled trial was conducted at Dr. Soetomo General Academic Hospital in Indonesia, from March to May 2022. The study aimed to assess the impact of a single dose vitamin D3 supplementation on serum IL-8 levels in children diagnosed with pneumonia. The study was conducted in adherence with the Declaration of Helsinki, and ethical approval was granted by the Institutional Review Board of Dr. Soetomo General Academic Hospital (Protocol Number 0379/KEPK/III/2022).

*Study population*

Children aged 1 to 60 months admitted with a clinical diagnosis of pneumonia were screened for eligibility. Exclusion criteria included children who had received vitamin D3 supplementation within four weeks prior to hospital admission, had received antibiotic prior to admission, or had any underlying conditions such as congenital disease or renal disorder. Prior to enrollment, the parents or guardians of each participant provided written informed consent.

*Intervention*

Eligible participants were randomized into either the intervention group (vitamin D3 supplementation) or the control group (placebo) using a list randomizer generator. The randomization was carried out by an independent statistician, who provided the list to the pharmacy staff. The vitamin D3 and placebo supplements were identical and prepared by the pharmacy staff. The healthcare providers and participants were blinded to the group assignments. Children in the intervention group received a single oral or nasogastric dose of vitamin D3 100,000 IU on the first day of hospitalization, while the control group received a matching placebo. All participants received standard antibiotic therapy for pneumonia as per the hospital's treatment protocol.

*Data collection*

Blood samples were collected from each participant on the first and seventh days of hospitalization. Prior analysis blood samples were centrifuged for 5 minutes at 3000 rpm. DBC Diagnostic Biochem Canada Inc.'s 25(OH)D ELISA kit (catalog number CAN-VD-510) and the human IL-8 ELISA kit (catalog number E090Hu) were used for measuring the concentration of 25(OH)D3 and IL-8. Demographic data, clinical signs, and symptoms of pneumonia were documented and monitored. The criteria of pneumonia severity was defined by World Health Organization, consisting of two categories, pneumonia and severe pneumonia (20).

*Sample size calculation*

The minimum required sample size was calculated for paired numerical data. The standard deviations and clinically significant difference were determined based on a previous study. Since no prior research has examined IL-8 levels in pediatric pneumonia, we referenced a different study examined IL-8 in diabetic patients (21). The standard deviations for the two measurements were 31.4 and 23.1, respectively, with an assumed correlation coefficient (ρ) of 0.5. The clinically significant difference (Δ) was set at 22.4. Consequently, the minimum required sample size for this study was 13 participants per group.

$$\sigma_{\text{diff}} = \sqrt{\sigma_1^2 + \sigma_2^2 - 2 \cdot \rho \cdot \sigma_1 \cdot \sigma_2}$$

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \cdot \sigma_{diff}^2}{\Delta^2}$$

σ diff = standard deviation of the differences
$\sigma_1$ = standard deviation of the first measurement
$\sigma_2$ = standard deviation of the second measurement
ρ = correlation between the two measurements
$Z_{\alpha/2}$ = z value for a 5% significance level (α = 0.05)
$Z_{\beta}$ = z value for 80% power (β = 0.20)
Δ = clinically significant difference

*Statistical analysis*

SPSS software, version 23.0 (IBM Corp, Armonk, NY, USA), was used to analyze the data. When reporting descriptive statistics, categorical variables were expressed as frequency and percentage, and continuous variables were expressed as median (interquartile range [IQR]). Data normality was assessed using the Shapiro-Wilk test. Between-group comparisons were conducted using the Chi-squared test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Pre- and post-intervention comparisons were analyzed using the Wilcoxon Signed-Rank test. Correlations between 25(OH)D levels and IL-8 levels were evaluated using Spearman's correlation coefficient. Statistical significance was set at $p<0.05$.

## Results

A total of 45 children were enrolled in the study, with 22 participants assigned to the placebo group and 23 to the supplementation group (Table 1). The age and sex distributions were not significantly different between the groups (p=0.116 and p=0.833, respectively). However, there was a significant difference in the weight-for-age distribution, with more underweight children in the placebo group (p=0.015). No significant differences were observed in height-for-age (p=0.167) or weight-for-height (p=0.738) between the groups. The clinical parameters, including respiratory rate and body temperature were similar between the groups, while oxygen saturation was slightly higher in the supplementation group (p=0.047). The category of pneumonia severity was comparable between groups.

The baseline levels of 25(OH)D3 were similar between the placebo (27.3 ng/mL) and supplementation (26.9 ng/mL) groups (p=0.856) (Table 2). After intervention, the median 25(OH)D3 levels in the supplementation group increased to 35.7 ng/mL, compared to 24.8 ng/mL in the placebo group; however, the difference was not statistically significant (p = 0.276). Within-group analysis showed 25(OH)D3 levels in the supplementation group increase significantly after intervention (p=0.048), while no significant increase was observed in the placebo group (p=0.884).

The baseline IL-8 levels were comparable between the placebo (5.1 pg/mL) and supplementation (7.4 pg/mL) groups (p=0.910) (Table 3). After intervention, IL-8 levels increased in both groups, but there was no difference between groups (p=0.329). Within-group analysis showed no significant change in IL-8 levels after intervention for both placebo and supplementation group (p=0.082; p=0.224, respectively).

## Discussion

This double blind randomized controlled trial revealed the effect of vitamin D3 supplementation on 25(OH)D3 and IL-8 levels in children with pneumonia. Our findings demonstrated that a single dose of 100,000 IU vitamin D3 significantly elevated 25(OH)D3 levels in the supplementation group, with the median of post-intervention levels exceeding 30 ng/mL, the threshold for vitamin D sufficiency. This result aligns with previous studies that have mentioned the efficacy of high-dose vitamin D3 in rapid correction of deficiency in pediatric populations (22, 23). While vitamin D supplementation effectively corrected deficiency in children with pneumonia, it did not significantly impact IL-8 levels. Our findings suggest that a single high-dose intervention may not be sufficient to alter the IL-8-mediated inflammatory response during acute pneumonia episodes. This could be because the timing of vitamin D3 administration may have missed the early phase of immune modulation during the initial inflammatory response (24). Previous research suggests that pre-existing vitamin D sufficiency,

**Table 1.** Baseline Characteristics of Study Participants

| Variables | Placebo (n=22) | Supplementation (n=23) | p-value |
|---|---|---|---|
| **Age (year)** | | | 0.116 |
| 1 | 17 (37.8) | 9 (20.0) | |
| 2 | 2 (4.4) | 4 (8.9) | |
| 3 | 1 (2.2) | 4 (8.9) | |
| 4 | 0 (0.0) | 2 (4.4) | |
| 5 | 2 (4.4) | 4 (8.9) | |
| **Sex** | | | 0.833 |
| Female | 7 (15.6) | 8 (17.8) | |
| Male | 15 (33.3) | 15 (33.3) | |
| **Weight-for-age chart** | | | 0.015 |
| Severe Underweight | 9 (20.0) | 9 (20.0) | |
| Underweight | 9 (20.0) | 2 (4.4) | |
| Normal | 4 (8.9) | 12 (26.7) | |
| **Height-for-age chart** | | | 0.167 |
| Severe Stunted | 9 (20.0) | 6 (13.3) | |
| Stunted | 6 (13.3) | 3 (6.7) | |
| Normal | 7 (15.6) | 14 (31.1) | |
| **Weight-for-height chart** | | | 0.738 |
| Severe Wasted | 6 (13.3) | 5 (11.1) | |
| Wasted | 2 (4.4) | 3 (6.7) | |
| Normal | 14 (31.1) | 13 (28.9) | |
| Overweight | 0 (0.0) | 2 (4.4) | |
| Respiratory Rate (/min) | 43.0 (39.5-50.0) | 40.0 (36.0-52.0) | 0.361 |
| Temperature (°Celcius) | 38.1 (38-38.6) | 38.3 (38.0-38.5) | 0.530 |
| Oxygen Saturation (%) | 97.5 (96.0-98.0) | 98.0 (97.0-99.0) | 0.047 |
| **WHO Severity Score** | | | 0.672 |
| Pneumonia | 9 (20.0) | 8 (17.8) | |
| Severe Pneumonia | 13 (28.9) | 15 (33.3) | |

*Significant p-value<0.05

rather than acute supplementation, may be more effective in preventing excessive inflammatory responses (25). Prior study demonstrated the downregulation of IL-8 production by vitamin D in macrophages derived from patients with cystic fibrosis (26). This effect was not mediated through the regulation of the vitamin D anti-inflammatory gene DUSP1, indicating that vitamin D exert its anti-inflammatory effects by other alternative pathways. Despite these findings, the downregulation of IL-8 was only achieved with vitamin D concentrations significantly higher than those typically found in vivo, suggesting that the therapeutic modulation of IL-8 in clinical settings might be challenging (26). Additionally, individual variability in the expression of vitamin D-related genes, such as CYP27B1 and VDR, may lead to differential responses to vitamin D supplementation (27). The findings from bovine studies emphasize the necessity of long-term vitamin D supplementation to fully assess its benefits on the immune system (28). Seven

**Table 2.** Groups Comparison on Vitamin D Levels

| 25(OH)D3 Levels (ng/mL) | Placebo | Supplementation | p-value[a] |
|---|---|---|---|
| **All Cases** | | | |
| Pre-intervention, Median (IQR) | 27.3 (21.9-33.1) | 26.9 (19.2-31.1) | 0.856 |
| Post-intervention, Median (IQR) | 24.8 (21.6-36.2) | 35.7 (22.7-48.2) | 0.276 |
| p-value[b] | 0.884 | 0.048* | |
| **Pneumonia** | | | |
| Pre-intervention, Median (IQR) | 28.8 (21.0-32.7) | 27.3 (23.5-30.9) | 1.000 |
| Post-intervention, Median (IQR) | 27.1 (23.1-42.6) | 37.2 (24.3-97.4) | 0.386 |
| p-value[b] | 0.441 | 0.208 | |
| **Severe Pneumonia** | | | |
| Pre-intervention, Median (IQR) | 24.9 (22.7-33.8) | 25.9 (18.4-31.1) | 0.872 |
| Post-intervention, Median (IQR) | 23.0 (18.5-30.5) | 35.7 (17.5-44.1) | 0.475 |
| p-value[b] | 0.650 | 0.191 | |

a, mann-whitney test; b, wilcoxon signed rank test; c, between pre- and post- intervention; *significant p-value<0.05

**Table 3.** Groups Comparison on IL-8 Levels

| Interleukin-8 (pg/mL) | Placebo | Supplementation | p-value[a] |
|---|---|---|---|
| **All cases** | | | |
| Pre-intervention, Median (IQR) | 5.1 (2.2-13.9) | 7.4 (2.7-12.3) | 0.910 |
| Post-intervention, Median (IQR) | 12.6 (2.9-22.8) | 10 (1.8-24.2) | 0.329 |
| p-value[b] | 0.082 | 0.224 | |
| **Pneumonia** | | | |
| Pre-intervention, Median (IQR) | 5.0 (2.1-15.8) | 8.9 (3.6-14.3) | 0.773 |
| Post-intervention, Median (IQR) | 19.5 (2.1-91.4) | 6.8 (2.8-10.3) | 0.290 |
| p-value[b] | 0.086 | 1.000 | |
| **Severe Pneumonia** | | | |
| Pre-intervention, Median (IQR) | 5.2 (2.5-13.6) | 6.7 (1.9-12.3) | 0.747 |
| Post-intervention, Median (IQR) | 11.1 (2.8-18.9) | 10.6 (1.2-26.7) | 0.800 |
| p-value[b] | 0.463 | 0.140 | |

a, mann-whitney test; b, wilcoxon signed rank test; c, between pre- and post- intervention

months supplemention of vitamin D in calves population exhibited significant alterations in the expression of various immune-related genes compared to control. This prolonged supplementation period revealed that vitamin D modulates both pro-inflammatory and anti-inflammatory pathways, including reduced IL-8 expression across different immune challenges. These observations suggest that short-term studies may not capture the complete effect of vitamin D, and sustained supplementation might be essential to achieve a stable modulation of inflammatory responses and improve disease resistance (29). In this study, a single oral or nasogastric dose of 100,000 IU vitamin D3 was administered to children hospitalized with pneumonia. The use of 100,000 IU vitamin D3 is supported by previous studies, where this dosage was well-tolerated and

did not result in adverse effects such as hypercalcemia (13, 14). Trials involving children with HIV demonstrated that doses of 100,000 IU every two months did not result in excessive vitamin D levels or toxicity (30). Reports of vitamin D intoxication in infants generally describe cases receiving extremely large doses, ranging from 240,000 to 4,500,000 IU, far exceeding the doses used in therapeutic contexts (31). This study also highlights the importance of maintaining adequate vitamin D status through regular supplementation, particularly in high-risk populations, as a preventive strategy rather than as a therapeutic intervention during acute respiratory infections (32). Maintaining optimal vitamin D status is particularly crucial in children with pneumonia, as it has been associated with reduced disease severity and better clinical outcomes (33). Moreover, given the multifactorial risks associated with pneumonia severity, such as nutritional status and comorbidities, it is unlikely that vitamin D alone can substantially alter clinical outcomes without addressing other factors (34). Several limitations exist in our study. The observed differences in weight-for-age distribution between groups, despite randomization, warrant consideration. The higher proportion of underweight children in the placebo group could have influenced the inflammatory response and clinical outcomes independently of vitamin D status. Second, the relatively small sample size and short follow-up period may have limited our ability to detect subtle changes in IL-8 levels. Third, although randomization was used, small differences in baseline characteristics like age existed between groups. To improve balance between groups, future studies should consider stratified randomization or matching. Fourth, the clinical signs of vitamin D deficiency were not assessed in this study. Future research should explore the impact of different dosing regimens, including repeated or maintenance doses, and the role of pre-existing vitamin D status in modulating immune responses in pediatric pneumonia.

## Conclusion

In conclusion, while single high-dose vitamin D3 supplementation effectively improved vitamin D deficiency in pediatric pneumonia, it did not significantly alter IL-8 levels, suggesting limited effects on the acute inflammatory response. Optimal supplementation strategies are needed to enhance the health outcomes of pediatric patiens with vitamin D deficiency and respiratory infections.

**Ethical Approval:** Ethical approval was granted by the Institutional Review Board of Dr. Soetomo General Academic Hospital (Protocol Number 0379/KEPK/III/2022).

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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