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Effects of a single dose of vitamin D in septic children: a randomized, double-blinded, controlled trial

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Abstract

Objective: To assess the effects of a single dose of vitamin D on 25-hydroxyvitamin D (25OHD) levels and clinical outcomes in children with vitamin D deficiency (VDD) and sepsis.

Methods: In this randomized, controlled trial, eligible children with VDD and sepsis were assigned to receive one dose of 150,000 IU of cholecalciferol or placebo. Serum concentrations of 25OHD, angiotensin-II (Ang-II), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) were assessed at baseline and 8 days after treatment. The cardiovascular Sequential Organ Failure Assessment (cv-SOFA) score, septic shock incidence, duration of ventilation, and mortality were also examined.

Results: One hundred nine participants fulfilled the study requirements. The two groups had comparable baseline characteristics. Ang-II, IL-6, and TNF-α concentrations were all reduced after vitamin D supplementation. Furthermore, the cv-SOFA score (1.76 ± 0.8 vs. 2.3 ± 1.1) and incidence of septic shock (7% vs. 20%) were lower in the treatment group than in the control group. The duration of ventilation and mortality rates did not differ between two groups.

Conclusions: A single dose of vitamin D improved 25OHD levels and the incidence of septic shock in children with VDD and sepsis.

Keywords

Vitamin D, sepsis, children, outcome, critical care illness, nutrition

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Introduction

Vitamin D is a fat-soluble vitamin that acts as a precursor hormone. Its primary role is maintaining calcium homeostasis. Vitamin D is also a potent activator of the innate immune system,[1] and it may be integral for natural defense mechanisms against microbial invasion.[2] Several studies revealed an association between vitamin D levels and blood pressure.[3,4] Sepsis is a clinical entity that complicates severe infections. The degree of immune dysfunction is correlated with the severity of sepsis.[5,6] Because vitamin D-related pathways are involved in various endocrine, immunological, and endothelial functions, many clinical studies suggested that vitamin D deficiency (VDD) is associated with sepsis and septic shock.[7]

Growing evidence suggests that a significant proportion (50%–90%) of critically ill patients have low 25-hydroxyvitamin D (25OHD) levels upon admission to the intensive care unit.[8–11] In turn, suboptimal 25OHD levels appear to be associated with a higher risk of mortality in critically ill patients.[9–11] Unfortunately, little is known regarding the effects of vitamin D supplementation in such patients. Therefore, we conducted a clinical trial to investigate whether cholecalciferol administration could improve the clinical outcomes of critically ill children with sepsis and VDD.

The primary aim of the study was to assess the effect of a single dose of oral cholecalciferol on serial 25OHD levels. The secondary aim was to investigate the effects of dosing on markers of inflammation and clinical outcomes.

Subjects and methods

Study participants

Children aged $\leq$14 years with sepsis who were admitted to pediatric intensive care unit (PICU) within 24 hours underwent vitamin D level measurements. All children met the sepsis criteria according to the 2012 Surviving Sepsis Campaign,[12] and all had an estimated PICU stay of longer than 48 hours. Vitamin D levels $\leq$20 ng/mL (50 nmol/L) denoted VDD.[13] Children with sepsis and VDD were recruited in the study.

Patients were excluded if they had a known history of renal stones, a diagnosis of hypercalcemia within the past year, baseline serum total calcium levels >10 mg/dL, an established diagnosis associated with an increased risk of hypercalcemia, current vitamin D supplementation within 6 months, or a need for extracorporeal membrane oxygenation/blood purification support.

Ethics

The study was approved by the Ethics Committee of the Medical College of Zhengzhou University. All parents of the participants were informed of the aims, requirements, and risks of the study and were advised that they could withdraw their children from the study at any time. Written consent forms indicating their full knowledge of the study protocol were acquired from the parents before the study.

Study design

This was a prospective, double-blind, placebo, controlled trial conducted in a university-affiliated, tertiary care hospital of a developing country. Patients who met the inclusion criteria and whose parents provided consent were randomly assigned to two groups. Children in the treatment group received 3 mL of 5% glucose containing 150,000 IU of cholecalciferol (Xinyi, Shanghai, China), even if the diet had been suspended or their symptoms has been resolved. Children in the control

group received the same volume of 5% glucose. Both the treatment and control liquids were placed in identical bottles, and they had the same color, weight, smell, and taste.

The form and dose were chosen on the basis of the recommendation of a systematic review of 43 studies of cholecalciferol, which suggested that oral vitamin D administration is safer than intramuscular administration among critically ill children.[14] Another study illustrated that a single vitamin D dose of 150,000–200,000 IU can effectively normalize vitamin D levels and prevent hypercalcemia. Furthermore, patients receiving long-term administration of vitamin D or doses greater than 300,000 IU should be monitored for adverse effects, including hyperlipemia and suppressed parathyroid hormone activity.[15]

Excluding the administration of cholecalciferol, the standard care for the two groups was identical. All patients in the study received concomitant therapy, including antibiotics, as considered appropriate by the attending physician.

Randomization was performed using a computer-generated allocation schedule with a six-block design prior to beginning the study. A sealed envelope with information on each child's assigned group was provided. Three previously trained research assistants who were not part of the study team prepared the medicines for the nutritional unit. Neither the medical and nursing staff responsible for monitoring the children nor the researchers were aware of patient allocation. An independent person on the data safety monitoring board held two sealed envelopes that revealed the subject sequence without disclosing the treatment of other patients.

Before the start of the study and on day 8 after treatment, blood samples were collected into heparinized tubes. The serum was immediately stored at −80°C until analysis.

Outcome measures

Vitamin D status. 25OHD concentrations were assessed before treatment and 8 days after treatment using enzyme-linked immunosorbent assay (ELISA; Kexing, Shanghai, China). The sensitivity of the test is 0.1 ng/mL, and its reportable range is 2 to 50 ng/mL.

Inflammatory cytokines. Inflammatory cytokine levels were assayed during sepsis. The concentrations of angiotensin-II (Ang-II), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) were assessed on the day before treatment and 8 days after treatment via ELISA.

Cardiovascular Sequential Organ Failure Assessment (cv-SOFA) score and septic shock incidence. We checked the maximum level of vasopressor use for all patients during their PICU stay using the cv-SOFA score as follows: 0 to 1, no vasopressors; 2, dopamine dose <5 μg/kg/min; 3, dopamine dose of 5 to 15 μg/kg/min or norepinephrine/epinephrine dose <0.1 μg/kg/min; and 4, dopamine dose >15 μg/kg/min or norepinephrine/epinephrine dose >0.1 μg/kg/minute.[16]

Severe septic shock was defined as sepsis with cardiovascular organ dysfunction.[17]

Other clinical data. Baseline information on the patients included age, sex, etiological category, and the Pediatric Risk of Mortality (PRISM III) score. Other clinical outcome measures, including the duration of ventilation, length of stay in the PICU, and mortality, were also collected. No limitations were set concerning the type or mode of ventilation. Mortality in the study referred to the incidence of death during PICU hospitalization.

Adverse events. Episodes of vomiting, diarrhea, and symptoms related to vitamin D

intake were recorded daily during the study. Safety parameters on cholecalciferol tolerance, including serum calcium levels, liver function, and renal function, were detected once weekly.

Sample size and statistical analysis

The required minimum sample size was 50 patients per study group to obtain an average vitamin D level of 10 ng/mL in children with VDD and sepsis at the PICU,[18] a 40% increase in vitamin D levels,[19] and a two-sided test with 5% significance and 80% power. Assuming a 15% dropout rate, the target enrollment was 120 children. According to the hospital bed occupancy rate, the estimated duration for data collection was set at 2 years.

The data were expressed as individual values or the mean ± SD and analyzed using STATA 8.0 (Stata Corp, College Station, TX, USA). When the data were normally distributed and the variance was homogeneous, Student's *t*-test was used to compare differences between means. When the data were not normally distributed, Mann–Whitney's test was used. Two-way ANOVA was used to compare time-based measurements within each group. Dichotomous outcomes were analyzed using the chi-squared test. Reported *p*-values were two-tailed, and $p < 0.05$ denoted significance.

Results

Subjects' characteristics

Initially, 290 children with sepsis were screened for vitamin D levels, and 165 patients were diagnosed with VDD, including 65 with severe VDD. Of the children with VDD, 45 were excluded because they met the prespecified exclusion criteria or their parents refused participation. Finally, 120 children were randomly and equally assigned to the study groups. However, some patients in both groups were admitted with serious conditions, resulting in seven deaths before the study was completed, and one patient in the control group developed septic shock. Four parents discontinued treatment, and their children died of multiple organ dysfunction syndrome after discharge from the hospital (Figure 1).

One hundred nine patients were enrolled in the study, including 64 boys and 45 girls. The various sepsis etiologies from major to minor included respiratory, neurological, gastrointestinal, cardiovascular, trauma, and poisoning. No patients had a cv-SOFA score exceeding 2. No differences in patient demographics or clinical conditions, including age, sex, primary etiology, PRISM III score,[20] and vitamin D levels before enrollment, were detected between the groups (Table 1).

Primary outcomes

Analysis of vitamin D levels. Vitamin D levels were similar between the groups before treatment. Both groups exhibited significantly increased 25OHD levels 8 days after the intervention (both $p < 0.05$). However, vitamin D levels were significantly higher in the treatment group than in the control group after the intervention ($p < 0.05$, Table 2).

Secondary outcomes

Inflammatory variables. TNF-α and IL-6 levels were similar between groups before treatment, whereas their levels were significantly lower in the treatment group on day 8 after treatment (both $p < 0.05$). Ang-II levels were significantly higher in the control group than in the control group 8 days after treatment, whereas no differences were noted in its levels prior to treatment ($p < 0.05$, Table 3).

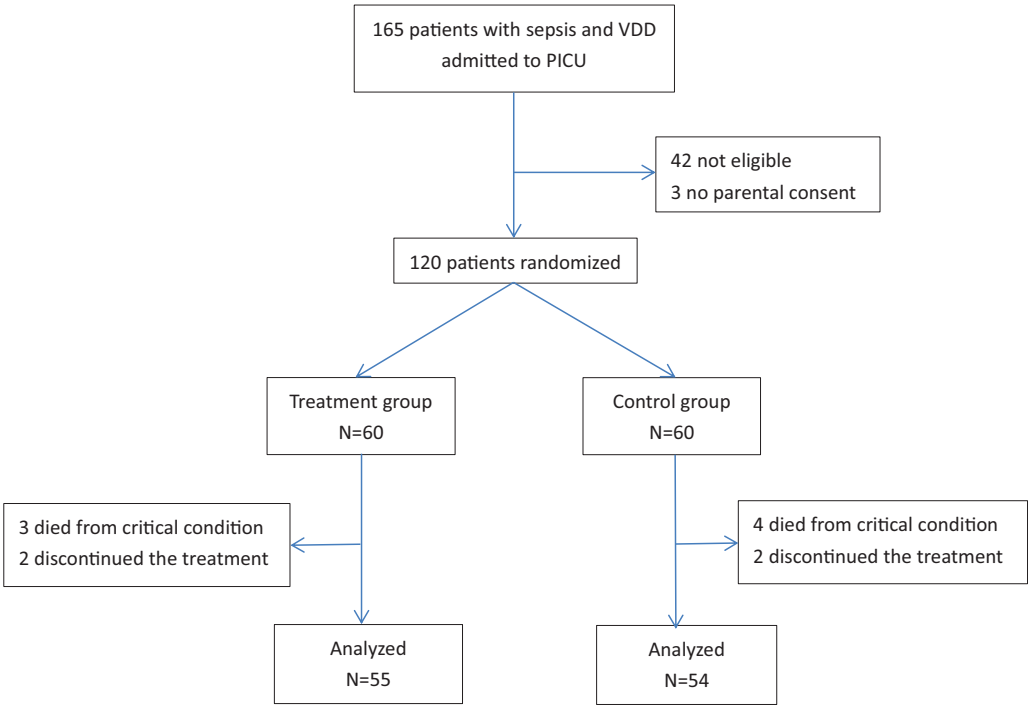

Figure 1. Study flowchart for children with sepsis and vitamin D deficiency.

Table 1. Baseline characteristics of the participants in both groups.

	Treatment group (n = 55)	Control group (n = 54)	*P*-value
Age (years)	3.9 ± 3.1	4.2 ± 3.2	0.7140
Gender (male/female)	33/22	31/23	0.783
Primary etiology			
Respiratory, n (%)	27 (49.1)	24 (44.4)	0.627
Neurologic, n (%)	17 (30.9)	21 (38.9)	0.384
Gastrointestinal, n (%)	7 (12.7)	5 (9.3)	0.563
Others, n (%)	4 (7.3)	4 (7.4)	0.978
PRISM III score	9.55 ± 2.7	9.94 ± 3.7	0.5258
25OHD (ng/mL)	12.2 ± 4.48	11.7 ± 4.3	0.6160
cv-SOFA score	1.88 ± 0.33	1.95 ± 0.21	0.2266

Data are presented as the mean ± SD unless otherwise indicated.
Abbreviations: PRISM, Pediatric Risk of Mortality; 25OHD, 25-hydroxyvitamin D; cv-SOFA, Cardiovascular Sequential Organ Failure Assessment.

cv-SOFA score and incidence of septic shock. The cv-SOFA score (1.76 ± 0.8 vs. 2.3 ± 1.1) and incidence of septic shock (7% vs. 20%) were significantly lower in the treatment group on day 8 after the intervention (both $p < 0.05$, Table 2).

Five days after starting the study, patients who received cholecalciferol exhibited shorter lengths of stay in the PICU than patients in the control group ($p < 0.05$). Although the duration of ventilation and mortality rate were lower among

Table 2. Vitamin D levels and clinical outcomes in both groups after treatment.

Group	25OHD (ng/mL)	cv-SOFA score	Septic shock n (%)	Duration of ventilation (days)	Length of stay in PICU (days)	Mortality n (%)
Treatment group	21.8 ± 4.3	1.76 ± 0.8	4 (6.7)	2.66 ± 5.3	11.47 ± 9.97	10 (16.7)
Control group	15.2 ± 3.7	2.3 ± 1.1	12 (20)	4.46 ± 8.1	12.5 ± 10.4	14 (23.3)
Mean (risk) difference (95% CI)	8.1662 (4.97, 8.16)	−0.54 (−0.94, −0.14)	−0.13 (−0.25, −0.01)	−1.8 (−4.86, 1.26)	−0.99 (−5.63, 3.65)	−0.067 (−0.21, 0.08)
p-value	0.0001★	0.0092△	0.0317▲	0.2454	0.6705	0.3613

Data are presented as the mean ± SD unless otherwise indicated.
Abbreviations: 25OHD, 25-hydroxyvitamin D; cv-SOFA, Cardiovascular Sequential Organ Failure Assessment; PICU, pediatric intensive care unit; CI, confidence interval
Note: ★△▲Significantly different between the treatment and control groups ($p < 0.05$).

children who received vitamin D, these outcomes did not significantly differ between the groups (Table 2).

Adverse events

Five patients reported vomiting and seven children exhibited diarrhea in the treatment group. Kidney injury was not found among the patients in the course of the study. However, no patient exhibited total hypercalcemia (serum calcium >2.75 mmol/L) or hypervitaminosis D (25OHD >200 nmol/L) during observation. Thus, no events were regarded as complications related to vitamin D.

Discussion

Studies have revealed that vitamin D is important for immunomodulation, inflammation and cytokine regulation, cell proliferation, cell differentiation, apoptosis, angiogenesis, muscle strength, and muscle contraction. VDD is highly prevalent in most PICUs worldwide, and it represents a major nutritional disorder in this population.[17] Its severity is mild/moderate in approximately 60% of patients and severe in nearly 36% of patients.[21] In our study, the average VDD rate was 56.9%, and that of severe VDD was 22.4%. The association of VDD with septic shock has been reported.[22] If VDD affects the incidence and resolution of septic shock, then vitamin D supplementation may divert attention from relatively simple, natural, and low-cost methods of preventing septic shock.

Vitamin D plays an important role in regulating the immune system because many cells of the innate and adaptive immune systems express vitamin D receptors.[23] VDD increases the risk of secondary infection in patients with sepsis, thereby increasing the incidence of bloodstream infections.[24] *In vitro* studies have revealed that vitamin D increases gene expression

Table 3. Changes of inflammatory cytokines in both groups.

	Ang-II (pg/mL)		IL-6 (pg/mL)		TNF-α (pg/mL)	
Group	before	after	before	after	before	after
Treatment group	243 ± 90.9	125 ± 64.9	554 ± 137.9	225.3 ± 125.9	485.4 ± 168.3	263.6 ± 121.8
Control group	251.6 ± 92	178 ± 89.1	584.8 ± 150.8	346.4 ± 167.7	512.2 ± 171.1	390.1 ± 146.4
p-value	0.6243	0.0006*	0.2691	0.0001★	0.4108	0.0001☆

Data are presented as the mean ± SD unless otherwise indicated.
Abbreviations: Ang-II, angiotensin II; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.
Note: *★☆Significantly different between the treatment and control groups ($p < 0.05$).

in immune cells[25] and enhances the production of many inflammatory factors, such as defensin, LL-37, reactive oxygen species, nitric oxide synthetase, and IL-1β.[26,27] Vitamin D can also regulate the balance between inflammation and tissue injury by inducing lymphocyte differentiation and development. TNF-α and IL-6 are important inflammatory cytokines in the inflammatory cascade.[12] Our study found that after the TNF-α and IL-6 levels were significantly reduced by vitamin D supplementation in children with sepsis, indicating that systematic inflammation was effectively alleviated in children in the treatment group, and vitamin D prevented the exacerbation of inflammation. Furthermore, the incidence of septic shock was decreased by 64% in the vitamin D treatment group, which suggested that vitamin D is necessary for controlling excessive inflammation; thus, it helped to prevent septic shock and protected against this crisis.

Vasopressor therapy is required to sustain life and maintain perfusion in life-threatening hypotension during shock, even with unresolved hypovolemia.[14] The intensity of septic shock-induced vascular hyporesponsiveness to vasopressors is closely associated with septic shock severity and evolution.[28] With the specificity, sensitivity, and widespread availability of laboratory tests, SOFA scores can be used to estimate refractory shock and can be obtained early with simple parameters.[29,30] In our study, the cv-SOFA scores of patients with sepsis were significantly reduced by vitamin D treatment. Moreover, several clinical trials described the effect of VDD on shock reversal (duration of vasopressor treatment or cumulative dosage),[31–33] possibly because vitamin D is more likely to alleviate an early blunted response to α-agonists and impaired endothelial reactivity to vasopressors. Additionally, low vitamin D levels affect blood pressure with changes in calcium homeostasis, resulting in endothelial dysfunction and increased arterial stiffness.[34,35]

As a factor in the renin–angiotensin system, Ang-II induces vascular endothelial injury by inducing inflammatory cytokine release and promoting vasomotor dysfunction and liquid leakage. Because Ang-II plays important roles in the development of sepsis, it is regarded as an important indicator of conditions in patients with sepsis. Our results illustrated that Ang-II levels decreased in children with sepsis after vitamin D administration, demonstrating that vitamin D can improve circulation and tissue perfusion by regulating Ang-II concentrations. Vitamin D modulates vascular tension, which contributes to its effects on septic shock and the differences among other nutrients.

Cholecalciferol supplementation may improve patients' ability to control

infection and recover from sepsis, including respiratory failure.[36] However, the duration of ventilation among patients with sepsis was not reduced by vitamin D supplementation in our study. Many other factors, such as primary disease, cardiac function, abdominal distension, and antibiotics, also contribute to weaning patients off ventilation,[37] and no single intervention strategy alone can improve the prognosis of sepsis. Our study also revealed no advantages of vitamin D supplementation on the length of PICU stay, possibly because of the low number of patients, different standards, or limited medical resources. Therefore, the role of vitamin D in treating sepsis remains controversial.

In the current study, although patients with sepsis who received vitamin D had a lower mortality rate, the difference was not significant between the groups. The biological mechanism by which vitamin D causes mortality may explain this finding. First, data from biochemical and molecular studies demonstrated that 1,25OH2D, the active form of vitamin D, plays a central role. Therefore, sufficient vitamin D activity can also be defined by the sufficient autocrine and paracrine production of 1,25OH2D.[38,39] Although cholecalciferol could provide a substrate for 1,25OH2D production, the promotion of serum 1,25OH2D levels is not guaranteed, which may compromise the benefits of cholecalciferol.[40] Second, because the manifestation of sepsis is greatly affected by physiological changes that occur with age,[29] the clinical variables used in the study vary with age. Although vitamin D has been demonstrated to affect mortality rates in critically ill adults,[41] whether it affects mortality rates in critically ill children is unclear. Finally, we did not follow our patients for a specific period, and we could not identify the potential benefit of vitamin D in the recovery and rehabilitation phase in the long term. An increasing number of surviving children in the PICU develop postintensive care syndrome with significant morbidity.[42]

In this randomized, controlled trial, we found that a single dose of 150,000 IU of cholecalciferol was safe and effective for rapidly improving circulating 25OHD levels and some clinical outcomes in children with sepsis. We found no adverse effects related to cholecalciferol administration during treatment. We also detected some biomarkers and provided underlying mechanistic evidence to explain why rapidly improving patients' vitamin D status could improve their clinical outcomes. In the future, these findings may support designing and implementing larger multicenter trials.

This study had several limitations. First, our primary aim was to assess whether a single dose of cholecalciferol could rapidly improve vitamin D status and enhance clinical outcomes in children with sepsis during hospitalization. This may have been insufficient for highlighting the long-term effects of vitamin D supplementation on critical illness. Second, we attempted to control differences in patients' baseline characteristics, but specific factors, such as underlying dysfunction in converting vitamin D to its active form and variable absorption through the alimentary tract, may have affected the observed outcomes. Additionally, fluid loading, renal loss of albumin, and inflammatory changes affect circulating 25OHD levels. These issues merit consideration when designing future trials to confirm and expand the current findings.

Conclusions

Administering 150,000 IU of cholecalciferol as a single dose at the onset of sepsis is a safe and effective intervention to rapidly improve 25OHD levels in children with VDD. Cholecalciferol supplementation also significantly decreased inflammatory

factor levels and improved the incidence of septic shock and cv-SOFA scores. More clinical trials are required to verify these findings and assess the optimal dose and method of vitamin D supplementation for critically ill children.

Contributor statement

Dr. Wang conceptualized and designed the study and held responsibility for the cholecalciferol components of the study. Together with Dr. Gao, Dr. Wang contributed equally to the coordination of the trial, assisted with interpretation of the data, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dr. Yang assisted with study design and development of the operational protocol. Dr. Cao assisted with the development of the operational protocol, supervised recruitment and data collection at one site, and reviewed the manuscript. Qianhan Wang served as the trial statistician, performed all the analyses, and reviewed the manuscript.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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