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ORIGINAL ARTICLE

Serum Vitamin D Status and Outcome among Critically Ill Children Admitted to the Pediatric Intensive Care Unit in South India

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Abstract
Objectives To determine the vitamin D status and the association between vitamin D status and the clinical outcome of critically ill children admitted to pediatric intensive care unit (PICU) in South India.
Methods Fifty-four consecutive children with medical and surgical diagnoses were included with parental consent. Severity of illness was assessed using PIM-2 score; Sequential Organ Failure Assessment Cardiovascular Score (CV-SOFA) was used to describe vasopressor use. Serum for 25(OH) D levels was obtained as close as possible to the ICU admission. Vitamin D deficiency was defined as serum 25(OH) D level <20 ng/ml (50 nmol/L). Primary outcome measures were serum 25(OH) D level and in-hospital all cause mortality. Secondary outcomes were illness severity, vasopressor requirement, use of mechanical ventilation and duration of ICU stay.
Results Of the 54 children, two were excluded due to insufficient serum for vitamin D analysis. Median age was 17.5 mo (IQR=4.5–78); 38.5 % were infants. Higher age was associated with low vitamin D levels (r_s=−0.34; p 0.01). Median serum 25(OH) D level was 25.1 ng/ml (IQR=16.2–34.2). Shock (30.8 %), CNS conditions (23.1 %) and respiratory illnesses (21.2 %) were the three most common reasons for admission to the PICU. Vitamin D deficiency was seen in 40.3 % of the critically ill children. Higher PIM score or SOFA score were associated with low vitamin levels (r_s=−0.29, p 0.04 and r_s=−0.29, p 0.05 respectively). Children who were mechanically ventilated had a significantly lower median serum 25(OH) D level than those who were not on ventilation [19.5 ng/ml (IQR=14.6–27.7)] *vs*. 32.1 ng/ml[(IQR=16.5–50.9), p 0.01]. Serum 25(OH) D level was also positively associated with serum calcium levels (r_s=0.32, p 0.03). The proportion of children who died or were discharged terminally at parental request was 23.8 % among those with serum 25(OH) D level <20 ng/ml as compared to 16.1 % among those with serum 25(OH) D level >20 ng/ml (p 0.49).
Conclusions Vitamin D deficiency is common among pediatric patients admitted to PICU in South India. Low serum 25(OH) D level was associated with higher severity of illness, need for mechanical ventilation, more vasopressor use and lower serum calcium levels. No association between vitamin D status and mortality was demonstrated.

Keywords Vitamin D · Critically ill children

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Introduction

Vitamin D, which was until a few decades ago thought of only in relation to bone health and calcium homeostasis, is currently being increasingly researched for its potential role in health and disease beyond bone metabolism [1].

The discovery that most tissues and cells in the body have vitamin D receptors and that several possess the enzymatic machinery to convert the primary circulating form of vitamin D, 25-hydroxyvitamin D, to the active form, 1,25-

dihydroxyvitamin D metabolite, has provided new insights into the function of this vitamin [2]. Vitamin D affects cardiovascular function, innate immunity and cell growth and proliferation and its deficiency has been associated with many diseases including lower respiratory infections, autoimmune diseases, cardiovascular diseases and cancer [2].

Vitamin D deficiency (serum 25(OH) D <20 ng/ml or 50 nmol/L) and insufficiency (serum 25(OH) D 20–30 ng/ml or 50–80 nmol/L) are reported in about 50 % of adults, and limited data support a higher prevalence in children [2]. Hypovitaminosis D is highly prevalent even in areas with adequate sunshine [1].

Studies from adult intensive care setting have shown vitamin D deficiency to be present in a significant proportion of critically ill adult patients and to be associated with poor outcomes [3–8]. The reported rates of prevalence of vitamin D deficiency among critically ill children varies from 30 to 70 % [9–12]. Vitamin D deficiency is associated with increased illness severity and generally results in longer hospital stays [10, 11] and biochemical evidence of lower calcium status [9, 10]. A definite effect on survival has not been identified in any of the pediatric studies.

Although vitamin D deficiency is reported to be common in India [13–15], with an estimated prevalence of 75–90 % [16] and vitamin D supplementation has been shown to improve outcome in chronically ill Indian children with moderate to severe asthma [17], there are no published studies on the association between vitamin D status and outcome in critically ill hospitalized children. Hence this study was designed to evaluate the vitamin D status and the impact of vitamin D deficiency on the clinical outcome of children admitted to the PICU.

Material and Methods

This prospective observational study was conducted among consecutive children with medical and surgical diagnoses admitted to the Pediatric Intensive Care Unit of Christian Medical College, Vellore, India from January 18 through February 8, 2013. The unit does not receive post-operative cardiac surgical patients. Those children whose parents were unwilling to participate, those transferred in from another intensive care unit and those with rickets were excluded from the study.

A sample size of 59 was calculated to show a prevalence of 40 % vitamin D deficiency among critically ill children with 95 % confidence limits and 12.5 % precision which could be carried out within the financial constraints. The data was based on relevant Indian studies that have estimated the prevalence of vitamin D deficiency in the general population [13–16].

Institutional Review Board (IRB) approval was obtained. Consent was taken from the parent after an explanation of the study at admission. The sources of information were study participants/relatives, hospital records and the laboratory reports.

After selection, data regarding the demographic profile, provisional diagnosis at the time of admission, past medical history, presence of an underlying chronic illness and medications were obtained. Details of intake of vitamin D and sun exposure were collected using standardardized questionnaire. Nutritional status was assessed by weight for age Agarwal criteria [18, 19].

Severity of illness was assessed using the PIM-2 score in the first hour after admission [20]. Sequential Organ Failure Assessment Cardiovascular Score (CV-SOFA) was used to determine the maximum level of vasopressor administered during PICU stay as follows: 0–1: no vasopressors 2. Dopamine <5 μg/kg/min 3. Dopamine 5–15 μg/kg/min or Norepinephrine/Epinephrine <0.1 μg/kg/min, and 4. Dopamine >15 μg/kg/min or Norepinephrine/Epinephrine >0.1 μg/kg/min [12, 21].

Serum sample for 25(OH) D measurement was obtained as close as possible to ICU admission, within 24 h. Vitamin D assay was done in the Clinical Biochemistry Department using electrochemiluminescence immunoassay on the automated Roch analyzer with a measuring range of 4–100 ng/ml. Reliability of the vitamin D assay was assured by running internal controls with every batch of test.

Vitamin D deficiency was defined as serum 25(OH) D less than 20 ng/ml (50 nmol/L) and insufficiency as serum 25(OH) D between 20 and 30 ng/ml [2, 22]. The primary outcome variables were serum 25(OH) D levels at admission to ICU and in- hospital all cause mortality. The secondary variables were illness severity, need for pressor medication, need for mechanical ventilation, serum calcium levels and duration of ICU stay.

Continuous variables were summarized using mean and standard deviations. Non-normally distributed continuous variables were summarized using median with interquartile ranges. Serum 25(OH) D levels were compared according to the clinical variables using Mann–Whitney *U* test or Kruskal-Wallis test, as appropriate. Dichotomous variables were compared between the two groups using chi-square or Fisher's exact test, as appropriate. Spearman rank correlation was used to examine the relationship between vitamin D levels and other clinical characteristics. STATA version 10.0 (StataCorp, College Station, Texas, USA) software was used for the data analysis.

Results

Of the 54 consecutive patients recruited, two were excluded due to insufficient serum for vitamin D analysis. The median age was 17.5 mo (IQR=4.5–78). The median serum

25(OH) D level was 25.1 ng/ml (IQR=16.2–34.2). Vitamin D deficiency (serum 25(OH) D <20 ng/ml) was seen in 40.3 % of the critically ill children. Vitamin D insufficiency (serum 25(OH) D 20–30 ng/ml) was seen in another 12 (23 %). Apart from the age which was associated with lower 25(OH) D levels, none of the baseline characteristics like gender, state of origin, nutritional status, presence of an underlying chronic condition and diagnosis were associated with a significantly lower serum (25OH) D level (Table 1).

A chronic disease condition involving major organ systems present in 16 (30.8 %) children were: oncologic (6), cardiac (3), rheumatologic (2), neurologic (1) endocrine (1), hepatic (1), immunodeficiency (1), and renal (1).

Shock (30.8 %), CNS conditions (23.1 %) and respiratory illnesses (21.2 %) were the three most common reasons for admission to the PICU. There was no association between 25(OH) D level and the clinical diagnoses on admission.

As shown in Table 2, higher vasopressor use and need for mechanical ventilation during the PICU stay were associated with lower vitamin D status. Twenty-one (40 %) children received vasopressors (CV-SOFA) during their PICU stay. Increasing vasopressor use correlated significantly with decreasing serum 25(OH) D levels (r_s=−0.29, p 0.05, Fig. 1). Vitamin D level was also positively associated with serum calcium levels (r_s=0.32, p 0.03). PIM-2 score was inversely correlated with serum 25(OH) D level (r_s=−0.29, p 0.04).

The median duration of mechanical ventilation was 3 d (IQR=2–5). Children who were ventilated during their PICU stay had a significantly lower median serum 25(OH) D level than those who were not ventilated [19.5 ng/ml (IQR=14.6–27.7)] *vs*. 32.1 ng/ml [(IQR=16.5–50.9), p 0.01].

Table 1 Baseline characteristics of vitamin D deficient and vitamin D non-deficient children

Characteristics	Number (%)	Serum 25(OH) D level (ng/ml)[a]		*P* value[b]
		<20	≥20	
Gender				
Male	31 (59.6)	14 (45.2)	17 (54.8)	0.394
Female	21 (40.4)	7 (33.3)	14(66.7)	
Age (years)				
<1	20 (38.5)	6 (30.0)	14 (70.0)	0.474
1–4	15 (28.8)	6 (40.0)	9 (60.0)	
5–12	12 (23.1)	7 (58.3)	5 (41.7)	
13+	4 (9.6)	2 (40.0)	3 (60.0)	
State of origin				
TN	32 (61.5)	12 (37.5)	20 (62.5)	0.828
AP	14 (26.9)	6 (42.9)	8 (57.1)	
Other	6 (11.5)	3 (50.0)	3 (50.0)	
Nutrition[#]				
<5th centile	11 (21.2)	0 (0)	1 (100.0)	0.603
5–75th centile	13 (25.0)	10 (37.1)	17 (62.9)	
75–97th centile	27 (51.9)	7 (53.9)	6 (46.1)	
>97th centile	1 (1.9)	4 (36.4)	7 (63.6	
Underlying chronic condition				
Yes	16 (30.8)	14 (38.9)	22 (61.1)	0.742
No	36 (69.2)	7 (43.8)	9 (56.2)	
Diagnosis				
Respiratory	11 (21.2)	3 (27.3)	8 (72.7)	0.765
Shock	16 (30.8)	8 (50.0)	8 (50.0)	
CNS conditions	12 (23.1)	5 (41.7)	7 (58.3)	
Cardiac conditions	5 (9.6)	1 (20.0)	4 (80.0)	
Post-operative	6 (11.5)	3 (50.0)	3 (50.0)	
Hepatic	2 (3.9)	1 (50.0)	1 (50.0)	

[a] n(%)

[b] Testing for association with serum 25(OH) D level by chi-square test

[#] Weight for age below the 75th centile on the Agarwal chart (Agarwal DK and Agarwal KN –Physical growth of affluent Indian Children. Indian Pediatr. 1994;31;377)

Table 2 Vitamin D levels among critically ill children according to the clinical characteristics

Characteristics	Number (%)	Serum 25(OH) D level[a]	*P* value[b]
PIM2 score			
0.1–1.0	13 (25.0)	24.5 (16.5–32.5)	0.12
1.1–2.0	15 (28.8)	30.5 (13.4–41.0)	
2.1–7.0	12 (23.1)	28.5 (17.7–40.5)	
7.1+	12 (23.1)	16.6 (7.8–24.6)	
CV – SOFA score			
1/2	31 (59.6)	27.4 (16.5–40.2)	0.05
3	16 (30.8)	21.7 (16.4–35.3)	
4	5 (9.6)	9.2 (3.2–13.0)	
Outcome			
Alive	42 (80.8)	26.0 (16.4–34.9)	0.39
Died/DAMA	10 (19.2)	19.8 (4.0–30.5)	
Serum calcium level			
<8	5 (11.9)	17.8 (13.4–26.8)	0.52
≥8	37 (88.1)	26.4 (16.4–24.5)	
ICU days			
1	13 (25.0)	25.6 (16.4–41.0)	0.31
2	17 (32.7)	29.4 (20.8–38.6)	
3	6 (11.5)	19.9 (16.4–24.5)	
4+	16 (30.8)	17.6 (8.6–32.9)	
Mechanical ventilation			
No	25 (48.1)	32.1 (16.5–50.9)	0.01
Yes	27 (51.9)	19.5 (14.6–27.7)	
Clinical infection			
No	20 (38.5)	25.1 (16.2–31.9)	0.98
Yes	32 (61.5)	24.4 (15.5–36.8)	
High CRP			
No	34 (80.9)	26.6 (16.4–38.6)	0.56
Yes	8 (19.1)	17.3 (16.5–32.2)	
Microbiological confirmation			
No	40 (76.9)	26.6 (16.4–36.1)	0.14
Yes	12 (23.1)	17.5 (6.5–32.2)	

DAMA Discharged terminally at parental request; *CRP* C-reactive protein; *PIM2* Pediatric index of mortality 2; *CV-SOFA* Sequential organ failure assessment cardiovascular score

[a] Median (inter quartile limits)

[b] Testing for association with serum 25(OH) D level by Mann–Whitney test (dichotomous) and Kruskal-Wallis test (multicategory characteristics)

Ten (19.2 %) children either died in the intensive care unit or were discharged terminally ill at parental request. Their median serum 25(OH) D level was lower than those who survived, but the difference was not statistically significant (19.8 ng/ml *vs*. 26.0 ng/ml, *p* 0.39). A higher proportion of children (23.8 %) either died or were discharged terminally at parental request among the children with serum 25(OH) D level <20 ng/ml than those (16.1 %) with serum 25(OH) D ≥20 ng/ml, but the difference was not statistically significant (*p* 0.49). The trend towards a lower 25(OH) D level among children with longer ICU stay also did not achieve statistical significance (r_s=−0.18, *p* 0.19).

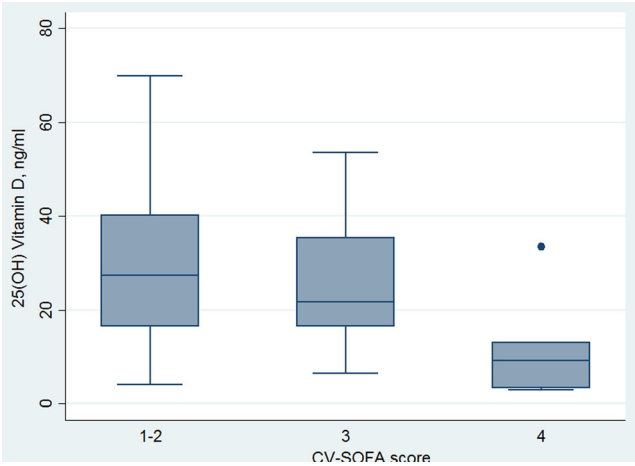

Fig. 1 Correlation between vasopressor use and vitamin D levels

Thirty-two (61.5 %) children were clinically presumed to have an infection. Microbiological confirmation was present in 12 (37.5 %) of them. The median 25(OH) D level among those with clinical infection was not different from those children who were not thought to have a clinical infection [24.4 ng/ml (IQR=15.5–36.8) *vs*. 25.1 ng/ml (IQR=16.2–31.9), *p* 0.98]. The median serum 25(OH) D level of the 12 children with microbiological confirmation of an infection was also not different from those without microbiologically confirmed infection [17.5 ng/ml (IQR=6.5–32.2) *vs*. 26.6 ng/ml (IQR=16.4–36.1), *p* 0.14].

Discussion

In this study, the prevalence of vitamin D deficiency (serum 25-OHD level <20 ng/ml or 50 nmol/L) among critically ill children admitted to a tertiary PICU in South India was 40.3 %. Another 23 % of children had vitamin D insufficiency (serum 25-OHD 20–30 ng/ml). This is higher than the reported prevalence of 29.5 % 25(OH) D levels <20 ng/ml from Brazil [9], but comparable to the reported rates of 34.5 and 40.1 %, among critically ill Australian and Canadian children respectively and lower than the prevalence of 69 % reported by Madden et al. from North America [12]. To the authors' knowledge, this is one of the first publication on vitamin D status of critically ill children from Indian PICUs.

The prevalence of vitamin D deficiency in 40.3 % of the index patients is lower than expected, considering that its prevalence among healthy Indian children has been shown to be high [13–15]. In Delhi, over 80 % of young children (9–30 mo of age) from two slum areas had serum 25(OH) D

values <14 ng/ml (35 nmol/L) [13]. Among Delhi school children (10–18 y of age), hypovitaminosis D (serum 25(OH) D <20 ng/ml) was seen in 92.6 % of the low socioeconomic group and 84.9 % of the upper socio economic group with over a third of them having 25(OH) D values <9 ng/ml [14]. Prevalence of biochemical hypovitaminosis D [serum 25(OH) D <20 ng/ml or <50 nmol/L] was seen in 90·8 % of girls from Delhi in yet another study [15]. However the prevalence of vitamin D deficiency among healthy children in South India has not been well documented.

Nearly 40 % of the study population were infants; 88 % of them originated from the two southern states of India. Majority (88 %) of the patients had medical illnesses with only 11.5 % being post-operative surgical patients. The patient characteristic was largely representative of the regular ICU population except for the Dengue fever and Scrub Typhus which are the two most common tropical fevers that are seen in the present institution from June through November. Although the data collection during a 1 mo period in January-February eliminates the effect of season, it does not provide information on seasonal variation in vitamin D status.

The index study population was different from the reports from western countries in that they were a younger population with a lower proportion (11.5 %) of surgical patients. Seventy percent of the children reported by McNally et al. [11] from Canada had a surgical diagnosis while 66.4 % of the 316 children in the Melbourne study [10] were post-operative cardiac-surgical patients. Furthermore, while 82 % of the children reported by Madden et al. [12], 61 % of McNally's patients [11] and 64 % of the 106 general medical patients reported by Rippel et al. [10] had an underlying chronic disease, only 30.8 % of the present patients had underlying chronic disease similar to the 39.7 % of the children reported by Rey et al [8]. It is conceivable that the differences in the characteristics of patients enrolled in the different studies might influence the relationship between vitamin D status and outcome.

Strengths of this study include recruitment of very consecutive patient admitted to the intensive care unit and hence patients belonging to every subspecialty participated in the study. A prompt collection of blood samples soon after admission to the intensive care unit (within 24 h of admission) was ensured, in order to minimize the influence of factors contributing to the decline of serum levels of vitamin D following ICU admission. Limitation of the study is that the sample size was insufficient to determine the effects of multiple other factors that commonly exist in critically ill patients affecting patient outcomes. The sample size under each variable during subgroup analysis was also too small to perform tests of significance in a meaningful manner and restricted the interpretation of univariate analysis. Despite this limitation, the authors could demonstrate that low vitamin D levels were associated the severity of illness and the vasopressor use. Serum 25(OH) D level was inversely correlated with admission PIM-2 score and vasopressor use (CV-SOFA score) and use of mechanical ventilation and was positively associated with serum calcium levels.

Our findings are similar to those of the North American studies that demonstrated 25(OH) D levels at admission to be inversely associated with PRISM III score on admission among PICU patients [11, 12]. However, no such association was observed between vitamin D status and predicted PRISM III and PIM 2 score in the Australian [10] and South American studies [9]. Among Australian PICU children, hypovitaminosis D was not associated with age, weight, gender, presence of chronic disease, need for mechanical ventilation, hypotension or hypertension, need for vasoactive support, ICU or hospital length of stay, higher admission PIM2 score, or death [10]. Among Brazilian PICU patients, hypovitaminosis D was also not associated with higher prediction of mortality risk scores, length of stay, and inotropic or respiratory support [9].

Vitamin D deficiency's effect on the patient outcomes such as higher mortality and/or longer PICU stay could not be demonstrated. Although vitamin D deficiency has been shown to be independently associated with all-cause mortality in critically ill adults, a definite effect on survival has not yet been demonstrated in any of the reported pediatric studies [9–12].

Although 64 % of the children were clinically infected and microbiological confirmation was present in 37 % of them, the authors could not demonstrate an association between vitamin D status and infection in these groups of critically ill children. Vitamin D plays an important role in innate immune system regulation, however results of clinical trials on effect of vitamin D on sepsis are mixed and vitamin D's relationship to sepsis in the critically ill patients has not been clearly demonstrated even by adult trials that showed an effect of vitamin D on mortality [4–8, 23]. Braun et al. showed a significant association between low serum 25(OH) D concentrations and an increase in blood culture positivity [5]. This lack of association between vitamin D status and mortality from infection in observational studies in the literature might be a result of study design or insufficient power to reveal a mortality difference [23].

In conclusion, the index study did not show an association between vitamin D status on admission to PICU and mortality but demonstrated that vitamin D deficiency is associated with severity of illness, need for vasopressor use and mechanical ventilation. Further studies in India on a larger number of PICU patients exploring the association of vitamin D with mortality, as well as prospective evaluations of the effect of vitamin D supplementation among critically ill children warrant urgent study.

Contributions KE: Designed the project, supervised patient care, was responsible for data collection & data management and drafted the manuscript; VJ: Performed the vitamin D assay; BA: Completed the statistical analysis; MN: Involved in patient care and assisted in data collection; AD

and MS: Provided intellectual support for the conception of the study and critically reviewed the manuscript. KE will act as guarantor for this paper.

Conflict of Interest None.

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