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ORIGINAL ARTICLE

Vitamin D Deficiency and Critical Illness

Shailender Prasad[1] · **Dinesh Raj**[1] · **Sumbul Warsi**[1] · **Sona Chowdhary**[1]

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Abstract
Objective To determine the prevalence of vitamin D deficiency in critically ill children and assess its association with severity of illness and other outcomes associated with critical illness.
Methods Eighty children aged 2mo to 12y, admitted with medical conditions to the pediatric intensive care unit of a tertiary care hospital were enrolled in this prospective observational study. Vitamin D levels were obtained during the first hour of stay. Severity score was assessed using the Pediatric Risk of Mortality III (PRISM III) within first 12 h of admission.
Results Vitamin D deficiency {25-hydroxy vitamin D [25(OH)D] levels<20 ng/ml} was observed in 67 (83.8 %) children. Vitamin D deficient children had significantly higher PRISM III score compared to vitamin D sufficient children [10 (IQR:5–15) *vs*. 6 (IQR:3–7); *p* 0.0099]. 25(OH)D levels had a significant negative correlation with PRISM III score (ρ -0.3747; *p* 0.0006).
Conclusions Vitamin D appears to be of utmost importance in critically ill children.

Keywords Vitamin D deficiency · Critically ill children · PRISM III score

✉ Dinesh Raj
dr_aiims@yahoo.co.in

[1] Department of Pediatrics, Holy Family Hospital, New Delhi 110025, India

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Introduction

Critical illness in children is a major cause of significant health care utilization and mortality around the world. The concern is especially understandable in developing countries with limited resources. Severe pneumonia, diarrheal diseases, severe malaria, sepsis, and meningo-encephalitis are some of the major causes of under-five mortality in our children [1]. Highly effective interventions are required if the Millennium Development Goal-4 (MDG-4) of reducing the under five mortality rate by two-third is to be attained.

Of late, there is considerable interest in the role of vitamin D in critically ill children and adults. Vitamin D is now known to be involved in many extra-skeletal pathways including immunomodulation, than just limited to bone mineralization [2–6]. Cells of the immune system express vitamin D receptors and exert the immune-modulatory action of vitamin D. The activity of Toll like receptors (TLRs), a part of the innate immunity, has cross-talks with vitamin D metabolic pathway [7]. Vitamin D is also involved in the secretion of LL-37 (cathelicidin), an antimicrobial peptide, needed for defense against microbes [8]. There is evidence that low vitamin D levels are associated with all cause mortality in adults [9]. Vitamin D deficiency is associated with sepsis and mortality in critically ill adults [10]. There is some evidence that low vitamin D level is a predictor of mortality in septic individuals [11].

Pediatric data on the prevalence of vitamin D deficiency in critically ill children and its association with the severity of illness is scarce [12–16]. The evidence of vitamin D status in critically ill children is lacking from developing countries especially India. The authors planned to prospectively evaluate the prevalence of vitamin D deficiency in critically ill children in India and assess its association with severity of illness and other outcomes associated with critical illness.

Material and Methods

The study was a prospective observational study and carried out at the pediatric intensive care unit (PICU) of a tertiary care center in New Delhi, India. The PICU is a seven bedded unit and caters to children with medical/surgical problems, and trauma. However, for the present study children admitted with only medical complaints were enrolled. Institutional review board approved the protocol. Written informed consent was obtained from the parents or guardians. Eighty children of the age group 2mo to 12y were enrolled from June 2013 through May 2014. The children were managed as per standard guidelines for the respective illness. Standard and relevant investigations (blood counts, C-reactive protein, blood culture, blood gas analysis, lactate, electrolytes, coagulopathy studies, chest radiograph, serum calcium, serum phosphate, liver and kidney function tests, *etc.*) needed for the management of the respective conditions were performed.

Vitamin D levels were obtained along with other routine sampling during the first hour of stay in the PICU. Vitamin D estimation was performed using a competitive chemiluminescent immunoassay (ADVIA Centaur Vitamin D total assay, Seimens Healthcare Diagnostics Inc, Tarrytown, NY). Vitamin D deficiency was defined as 25-hydroxy vitamin D [25(OH)D] levels less than 20 ng/ml. Severity score was assessed using the Pediatric Risk of Mortality III (PRISM III) within first 12 h of admission. PRISM III is a pediatric physiology based score for mortality risk [17].

Clinical and demographic variables were recorded using a structured performa. Child's vital parameters were monitored and documented. Need of vasopressors, respiratory support, and blood products was recorded. Presence of hypotension, dyselectrolytemia, hypoglycemia, septic shock, respiratory failure, and organ dysfunction were recorded.

Nutritional status was assessed using z-scores for weight for age, length or height for age, weight for length or height and BMI. Children were classified as wasted and stunted if weight for height and height for age, respectively, was below -2SD. Malnutrition was defined by presence of wasting or stunting in children under 5y of age and BMI less than<−2 SD in children above 5y of age.

Categorical variables were presented as proportions and continuous variables were presented as mean (±SD) or median (IQR). Children were divided into two groups: vitamin D sufficient [25(OH)D≥20 ng/ml] and vitamin D deficient [25(OH)D<20 ng/ml]. For comparisons between these two groups, t-test was used for normally distributed continuous variables, and Wilcoxon rank-sum test was used for non-normally distributed continuous variables. Chi square test or Fisher's exact test was used for categorical variables. A difference between three or more groups was performed using ANOVA or Kruskal-Wallis test. Spearman's correlation was used for correlation between 25(OH)D levels and PRISM III score. A p value of less than 0.05 was considered significant.

Results

Eighty children of age group 2mo to 12y were enrolled during the study period. The baseline characteristics of the enrolled children are given in Table 1. The median age and weight was 12 (IQR:5–66) mo and 9.6 (IQR:6–14) kg respectively. Median 25(OH)D levels were 12.1 (IQR:9.0–18.0) ng/ml. Median PRISM III score was 8 (IQR: 4.5–14). The PICU stay and total duration of hospitalization was 4 (IQR:3–6) d, and 7 (IQR:6–10) d respectively. Fifteen (18.8 %) children died of the illness. Eleven (13.8 %) children had culture positive sepsis. Inotropic support and mechanical ventilation was required in 30 (37.5 %) and 33 (41.3 %) children respectively.

Vitamin D deficiency [25(OH)D levels<20 ng/ml] was observed in 67 (83.8 %) children. Only 13 (16.3 %) children were vitamin D sufficient [25(OH)D levels≥20 ng/ml]. 25(OH)D levels had a significant negative correlation with PRISM III score (ρ -0.3747; p 0.0006) (Fig. 1). 25(OH)D levels did not correlate with duration of PICU stay and total duration of hospitalization. The children were categorized into three groups of increasing severity of illness based on PRISM III score (0–9, 10–19, ≥20). Table 2 shows the 25(OH)D levels in the three groups. Median vitamin D levels were 15.8 (IQR:10.1–20.2) ng/ml, 10.0 (IQR:9.0–15.3) ng/ml, and 7.2 (IQR:5.1–14.2) ng/ml in the 0–9, 10–19, and≥20 group respectively (p 0.0036).

Although median 25(OH)D levels were lower in the children who died compared to those who survived [9.9

Table 1 Baseline characteristics of the enrolled critically ill children

S. No	Characteristics	n=80
1.	Age, mo; median (IQR)	12 (5–66)
2.	Male gender; n (%)	55 (68.8)
3.	Weight, kg; median (IQR)	9.6 (6–14)
4.	25(OH)D levels, ng/ml; median (IQR)	12.1 (9.0–18.0)
5.	PICU stay, days; median (IQR)	4 (3–6)
6.	Duration of hospitalization, days; median (IQR)	7 (6–10)
7.	PRISM III score; median (IQR)	8 (4.5–14.0)
8.	Serum calcium, mg/dl; mean (±SD)	8.6 (±1.1)
9.	Serum phosphate, mg/dl; mean (±SD)	4.8 (±2.4)
10.	Positive blood culture, n (%)	11 (13.8)
11.	Mortality, n (%)	15 (18.8)
12.	Need of vasopressors, n (%)	30 (37.5)
13.	Evidence of coagulopathy, n (%)	31 (38.8)
14.	Need of mechanical ventilation, n (%)	33 (41.3)
15.	Need of steroids, n (%)	22 (27.5)

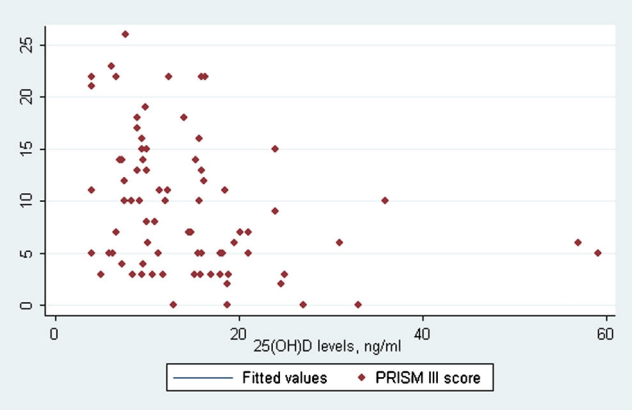

Fig. 1 Correlation between 25(OH)D levels and PRISM III score in critially ill children

(IQR:7.3–16.0) ng/ml *vs*. 13.0 (IQR:9.4–18.5) ng/ml], the difference was not statistically significant (p 0.18). Table 3 shows the 25(OH)D levels and PRISM III score in survivors and non-survivors.

The characteristics of vitamin D deficient and sufficient children were compared (Table 4). There was no difference in baseline variables (age, sex, weight, height, and socioeconomic status) between the two groups. Vitamin D deficient children had significantly higher PRISM III score compared to vitamin D sufficient children [10 (IQR:5–15) *vs*. 6 (IQR:3–7); p 0.0099]. The two groups did not differ in terms of duration of PICU stay, duration of hospital stay, culture positivity, biochemical parameters (serum calcium, serum phosphate), need of ventilation or steroids, presence of coagulopathy and mortality.

A significant proportion of children [35 (43.8 %)] were malnourished (Table 5). Though median vitamin D levels were higher in malnourished children compared to healthy children [15.6 (IQR:9.4–18.5) ng/ml *vs*. 10.9 (8.9–16.0) ng/ml; p 0.1443], the difference was not statistically significant. Malnourished children were not sicker than their normal counterparts as revealed by their PRISM III scores [6 (5–15) *vs*. 10 (4–14); p 0.7151]. Children with low, intermediate, and high PRISM III scores did not have different proportion of malnutrition (Table 2). Children with malnutrition were not at higher risk of mortality compared to normal children.

Table 2 Relationship between vitamin D levels, severity of illness and nutritional status

PRISM III score	25(OH)D levels, ng/ml; median (IQR)	Proportion of children with malnutrition; n (%)
0–9	15.8 (10.1–20.2)	22 (45.8)
10–19	10.0 (9.0–15.3)	29.2 (29.2)
≥20	7.2 (5.1–14.2)	6 (75.0)
p value	**0.0036**	0.069

Statistically significant associations have been made bold

Table 3 Comparison of 25(OH)D levels and PRISM III scores of survivors and non-survivors

	Non-survivors, n=15	Survivors, n=65	p value
Median 25 (OH)D levels, ng/ml	9.9 (7.3–16)	13.0 (9.4–18.5)	0.18
Median PRISM III score	14 (8–19)	7 (3–13)	**0.0061**

Statistically significant associations have been made bold

Discussion

Data from this prospective observational study suggests that majority (84 %) of children are deficient in vitamin D [25(OH)D levels<20 ng/ml] at admission. Available evidence suggests a prevalence ranging from around 30–75 % in critically ill children [12–16]. The exceptionally high prevalence in the index study was not unexpected, given the wide prevalence of vitamin D deficiency in India [18]. As authors' institution is accessed by all strata of the society, they presume that the data is representative of the society as a whole.

Vitamin D deficient children were significantly sicker compared to vitamin D sufficient children. Furthermore, 25(OH)D levels had a poor but significant negative correlation with PRISM III score. Relationship between 25(OH)D levels and severity scores has been evaluated earlier in few studies [12–16]. McNally et al. reported that with every additional point increase in PRISM III score, the likelihood of vitamin D deficiency increased by 8 % [12]. Somewhat similar observation was reported by Madden et al. who reported an OR of 1.19 (95 % CI 1.10–1.28) for a 1-quartile rise in PRISM III score per 5 ng/ml decrease in 25(OH) D levels [13]. However, some studies have not found an association between vitamin D deficiency and severity scores [14–16]. This inconsistent association could be explained by the heterogeneous patient population in different studies and variation in the tools used to assess severity. The authors have used PRISM III score which is a validated tool to predict mortality during the initial hours of hospitalization. The clinical significance of the negative correlation between vitamin D status and PRISM III score can only be ascertained from intervention trials when vitamin D supplementation translates into improved outcome and shorter PICU stay.

The authors did not find any difference in the duration of PICU stay or total duration of hospitalization between vitamin D sufficient and vitamin D deficient children. McNally et al. reported a significantly longer PICU stay (+1.92 d; p 0.03) in children with vitamin D deficiency [12]. They found that every 10 nmol/L decrease in 25(OH) D level was associated with increase in hospital stay by 0.44 d. This is likely to be true as children who are sicker at admission are likely to stay longer in hospital. Similar evidence has been found in adult medical as well as surgical patients [19,20]. The index study was, however, not adequately powered to examine this difference.

Table 4 Comparison of patients with vitamin D deficiency and sufficiency

	Characteristics	25(OH)D<20 ng/ml, *n*=67	25(OH)D≥20 ng/ml, *n*=13	*p* value
1.	Median age, mo (IQR)	12 (5–72)	13 (8–30)	0.96
2.	Male gender, n (%)	46 (68.7)	9 (6.9)	0.97
3.	Median weight, kg (IQR)	9.9 (6.3–14)	6.6 (4.8–10)	0.54
4.	Positive blood culture, n (%)	9 (13.4)	2 (15.4)	0.57
5.	Median PRISM III score (IQR)	10 (5–15)	6 (3–7)	**0.009**
6.	Serum calcium, mg/dl; mean (±SD)	8.6 (±1.1)	8.7 (±1.0)	0.83
7.	Serum phosphate, mg/dl; mean (±SD)	5.0 (±2.6)	3.9 (±1.0)	0.14
8.	Presence of coagulopathy, n (%)	28 (41.8)	3 (23.1)	0.17
9.	Need of ventilation, n (%)	30 (44.8)	3 (23.1)	0.13
10.	Presence of hypoglycemia, n (%)	13 (19.7)	1 (7.7)	0.28
11.	Need of steroids, n (%)	18 (26.9)	4 (30.8)	0.51

Statistically significant associations have been made bold

Adult studies have found a higher risk of mortality in patients with vitamin D deficiency [21–23]. However, pediatric studies have not found a difference in mortality between vitamin D sufficient and vitamin D deficient children. In the index study, 14 (20.9 %) children died in the vitamin D deficient group, but only one (7.7 %) died in the vitamin D sufficient group. The difference, however, was not statistically significant. The study was not powered sufficiently to assess the relationship between vitamin D status and mortality.

Theoretically, given the association of vitamin D with prediction of mortality scores [12,13], there appears to be role of vitamin D in successful outcome of a critical illness. The pleiotropic action of vitamin D on cells of the immune system (macrophages, lymphocytes, and dendritic cells) might provide protection from infections and immune-dysregulation in the critically ill patient. Vitamin D plays a key role in cardiovascular and metabolic (calcium, phosphate and glucose) pathways, which are often dysregulated in critical illness. There is some evidence to suggest that vitamin D affects lung function as well [24]. Data from NHANES III showed association between vitamin D levels and FEV1 and FVC [24]. Vitamin D deficiency is related to respiratory infections, acute exacerbations of asthma and cystic fibrosis, and acute lung injury [25–27].

None of the earlier studies in critically ill children have evaluated the association between nutritional status and vitamin D levels. The vitamin D levels were not different between malnourished and normal children. Malnourished children were neither more sick nor at an increased risk of dying compared to normally nourished children. The index study was, however not powered enough to compare these outcomes between malnourished and normally nourished children.

Table 5 Comparison of 25(OH)D levels and PRISM III scores of malnourished and normally nourished children

	Malnourished children, *n*=35	Normally nourished children, *n*=45	*p* value
Median 25 (OH)D levels, ng/ml	15.6 (9.4–18.5)	10.9 (8.9–16.0)	0.1443
Median PRISM III score	6 (5–15)	10 (4–14)	0.7151

Given all these diverse pleiotropic actions of vitamin D in a critically ill patient, it is likely that vitamin D is important in a sick child. Whether the low levels of vitamin D is an indicator of increased consumption in a sick child, or per se contribute to the severity of the illness, needs to be determined.

Despite having a small sample size, this study highlights the high prevalence of vitamin D deficiency and its association with severity scores in critically ill children. Vitamin D sufficiency may help in reduction of the severity of illness and ensure an optimal response to therapy in a critically ill child. With increasing availability of fairly accurate estimation of vitamin D deficiency, and ease of supplementation in case of deficiency, vitamin D supplementation is likely to become a highly effective intervention to reduce child morbidity and mortality.

The index study also has some limitations. Sample for vitamin D estimation was drawn at admission or within first hour of hospitalization. There have been some concerns on the timing of sampling as acute fluid shifts are likely to affect vitamin D levels [28]. Parathyroid hormone (PTH) levels were not performed in the present study. The children who were vitamin D deficient were supplemented with vitamin D as soon as they were clinically stable and able to take orally. This might have had some effect, however small, on the duration of PICU stay.

The study sensitizes the pediatric practitioner regarding the role of vitamin D deficiency in critically ill children. Although there are no guidelines regarding the routine evaluation of vitamin D in well or unwell children, targeted assessment of vitamin D status in at risk children is needed. A stricter

implementation of routine supplementation of vitamin D in exclusively breast fed babies and a high index of suspicion of vitamin D deficiency in older children on a case to case basis and its treatment is warranted [29].

Conclusions

This study highlights the high prevalence of vitamin D deficiency in critically ill children and its association with PRISM III scores in a developing country. Interventional studies are needed to establish the role of vitamin D in critically ill children.

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Conflict of Interest None.

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