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Research Paper

A Study on Vitamin D Level in Critically Ill Children Admitted in PICU at A Tertiary Care Hospital

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Abstract

Introduction: *Vitamin D is critical in bone metabolism and calcium homeostasis,as well as an important regulator in metabolic processes, cardiovascular and immune systems. It is crucial for humans to have sufficient vitamin D levels to maintain bone health and improve response to infection. Vitamin D deficiency (VDD) represent a potentially modifiable risk factor for greater illness severity and clinical outcome during critical illness.*

The objective of this study is to assess Vitamin D status in critically ill children admitted in PICU and to determine the frequency of VDD amongst them and its association with disease severity and important clinical outcomes.

Methods: *It was a prospective observational study conducted over a period of 6 months in the PICU of tertiary care hospital on 100 critically ill children aged 1 month –12 years. Serum Vitamin D levels were estimated within 24 hours of admission to PICU. Severity of illness was assessed using Pediatric Index of Mortality III (PRISM III) score. The need for catecholamines and mechanical ventillation, length of PICU stay and mortality were also recorded.*

Results: *The prevalence of VDD among critically ill children was 49%.Vitamin D level was significantly lower in VDD group as compared to 'no deficiency' group (16.3±2.5 vs 38±5.9, p value 0.01). There was also a trend toward increased disease severity, higher need of catecholamines and mechanical ventillation in VDD group. The length of PICU stay (pvalue0.004) and mortality rate (pvalue0.006) was also significantly higher in VDD group.*

Conclusion: *VDD is common in critically ill children and associated with greater illness severity, longer PICU stay and higher mortality.*

Keywords: *Critically ill children, Mortality, PICU, PRISM III, Vitamin D, Vitamin D deficiency.*

Introduction

Vitamin D is an essential hormone that is very important for optimal health. It is a fat soluble vitamin with key endocrine functions.[1] This pleiotropic hormone plays a major role in regulation of calcium metabolism, maintenance of bone integrity, cardiovascular system, and several pathways of immune system in general and innate immune system in particular.[2] It activates toll-like receptors in leukocytes →leading to induction of antimicrobial peptides that kill micro organisms (predominantly cathelicidin). 1,25(OH)2D3 exerts its molecular effects by binding to the vitamin D

receptor .Vitamin D and vitamin D receptor (VDR) expression and activity are associated with immunity against various infections and autoimmune diseases.[3] Levels of 25-hydroxy vitamin D (25(OH)D) are used to assess the adequacy of vitamin D stores in our body. Patients with levels less than 20 ng/mL are commonly categorized as vitamin D deficient [2,4] and treatment is initiated in children in order to prevent rickets [4]. Various studies across the world including India have estimated the prevalence of VDD in healthy children to be in the range of 10–90%.[4,5,6] Such a high prevalence of VDD may be the result of inadequate dietary intake of vitamin D, inadequate exposure to sunlight because of an indoor lifestyle, a high level of skin pigmentation.[7,8]

Any critical illness or injury disturbs the internal milieu of the body and may adversely affect the reserves of vital nutrients and minerals of the body. In addition, nutrition is often suboptimal in these group of patients and this, in turn, may further aggravate any deficiencies. Vitamin D deficiency has been reported to be widely prevalent in critically ill children from ICUs worldwide.[9-12]

So this study has been undertaken to estimate the prevalence of vitamin D deficiency in critically ill children admitted in PICU and also to investigate any association between VDD and important clinical outcomes including illness severity, requirement for ventilation and catecholamines, length of PICU stay and mortality.

Materials and Methods

Design and Settings

This was a prospective observational study conducted over a period of 6 months (July 2019 – December 2019) in children admitted to the pediatric intensive care unit (PICU) of our tertiary care hospital. The severity of illness was measured using the Pediatric Risk of Mortality III (PRISM III) score at admission to the PICU .The patients were followed up during their PICU stay and the following parameters were recorded: the need for mechanical ventilation and catecholamines, development of multiple organ dysfunction syndrome (MODS), septic shock, hypocalcaemia, the length of PICU stay and any mortality. Standard definitions were used for sepsis, septic shock and MODS. [13]

Participants

A total of 100 critically ill children aged 1 month to 12 years admitted in PICU were eligible for inclusion as cases.

Exclusion Criteria

Children who were already on vitamin D supplementation, or had received large doses for rickets or any documented vitamin D deficiency in the past 1 year, those on corticosteroids and children with any underlying chronic liver or kidney disease or had recent renal stones were excluded from the study.

Baseline demographic data such as age, gender, weight, cause of PICU admission, signs suggestive of severe acute malnutrition (SAM) (as defined by WHO)[14] were recorded

Ethics

The study was approved by the Institutional Ethical Committee .After obtaining informed written consent from the parents, the eligible children was enrolled in the study.

Vitamin D measurement

Venous blood samples (2.0 ml) were collected from all cases (within 24 hours of admission to the PICU) for analysis of serum 25(OH)D in the Central Composite Laboratory under Biochemistry Department of the institution.

VDD was defined as a level of 25(OH)D <20 ng/ml.[15] All the pediatric cases included in the study were divided into two groups as Vitamin D deficiency group (25[OH]D <20 ng/ml) and ‘no deficiency ‘ group(25[OH]D ≥20 ng/ml).

Outcome

1. The primary outcome measure was to estimate the prevalence of VDD in critically ill children admitted in the PICU of our tertiary care centre.

2. Secondary outcomes were to compare vitamin D-deficiency group and no deficiency group for severity of illness (PRISM III score), shock, MODS, need for mechanical ventilation and catecholamines, length of PICU stay and mortality.

Statistical Analysis

Data entry and statistical analyses were performed using Microsoft Excel 2010 and SPSS software version 20. Demographic variables were recorded as percentages, means, standard deviations (SD), medians and interquartile ranges (IQR), as applicable. Dichotomous outcomes were compared by using the x2 test. Continuous variables were compared by Student's t-test. A P value <0.05 was taken as significant.

Results

A total of 150 children admitted to the PICU during the study period were selected for the study. Out of them, 44 children were excluded due to pre-specified exclusion criteria and 6 children as their parents refused to give consent. So the final outcome was measured in 100 critically ill children. The study flowchart and recruitment are shown in Figure 1.

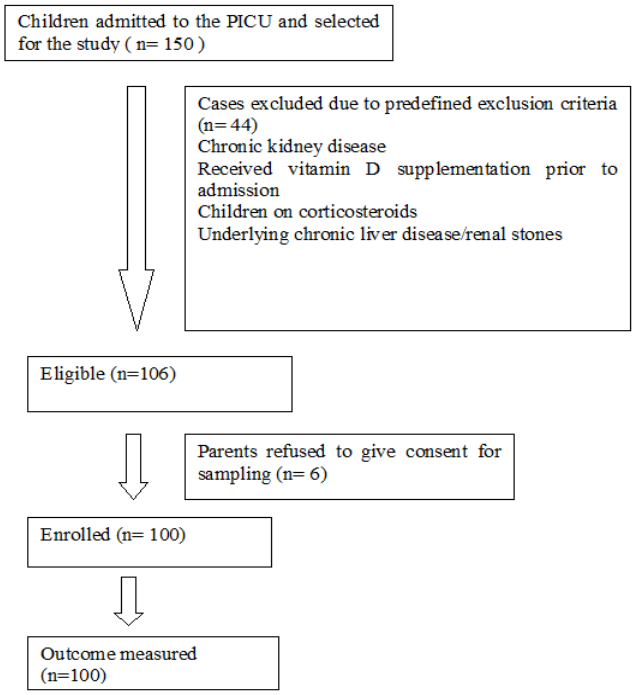

Figure 1: Study flow diagram for critically ill children

Baseline demographic and clinical data are described in the subsequent tables. The mean age of study population was 4 years (SD = 2.9).In terms of gender, there was a male preponderance (68%).

Table No 1: Age wise and gender wise distribution of critically ill children

Characteristics	Study population (n=100)
Age(years) ,mean ±SD	4 ± 2.9
Weight , kg, mean ±SD	13.4 ± 8.7
Male , n(%)	68(68)
Female ,n(%)	32(32)

Table No 2: Cause wise distribution of cases admitted in PICU

	Total cases=100
Cause	n (%)
Sepsis/ septic shock	39
Pneumonia/other respiratory diseases	26
CNS diseases	24
Cardiac illness	6
Gastrointestinal disease	5

Thus, the three leading cause of admission of cases to PICU was sepsis/septic shock (39 %), followed by pneumonia (26 %) and CNS diseases (32 %). (Table 2)

Table No 3: Prevalence of vitamin D deficiency (based on 25(OH) levels)

Study population, n=100 [25(OH)D levels , ng /ml]	
< 20, Vitamin D deficient ,n (%)	≥ 20, not deficient , n(%)
49/100 (49 %)	51/ 100 (51 %)

Thus, in our study, the prevalence of vitamin D deficiency among critically ill children was found to be 49%. (Table 3)

Vitamin D levels were significantly lower in vitamin D deficiency group as compared to 'no deficiency 'group. (p=0.01).

The severity of illness as assessed by **PRISM III score** was significantly higher in vitamin D deficient group (p value 0.003).

More cases with vitamin D deficiency had SAM compared to not deficient cases, but the difference was not statistically significant.

Also, the study showed an increased requirement of catecholamines in vitamin D deficient group as compared to 'no deficiency group', but the difference was not statistically significant. There was also a trend towards increased occurrence of septic shock, hypocalcaemia and MODS in VDD cases, but the difference was statistically insignificant. (Table 4)

The need for mechanical ventillation was significantly higher in children with vitamin D deficiency (40.8%, 20 of 49) as compared to 'no deficiency' group (31.3% , 16 of 51), however the difference was statistically insignificant. (p value =0.52).

The VDD group had a longer duration of PICU stay (7.5± 5.1 days) as compared to 'no deficiency' group (5.4 ± 3.2 days), and the difference was statistically significant (p value =0.004) (Table 5)

Lastly, when considering the outcome between the two groups, mortality rate was found to be significantly higher in those with vitamin D deficiency (Table 6)

Table No 4: Comparison of different variables between Vitamin D deficient and no deficiency group

Variables	Vitamin D deficient group ,n=49	'no deficiency group' ,n=51	P value
Serum Vitamin D Levels , mean ± SD	16.3± 2.5	38± 5.9	0.01
Severe acute malnutrition, n(%)	12 (25)	7 (13.4)	0.21
PRISM III score, median(IQR)	19(14-24)	15(14-24)	0.003
Required catecholamines ,n(%)	28(57.1)	22(43.1)	0.49
Hypocalcaemia , n(%)	14(28.5)	9(17.6)	0.36
Cause for admission—n(%)			
• Septic shock	23 (46.9)	16 (31.3)	0.28
• Pneumonia/other respiratory diseases	17 (34.6)	9 (17.6)	0.31
• CNS	14 (28.5)	10 (19.6)	0.11
• Cardiac illness	4 (8.1)	2 (3.9)	0.08
• Gastrointestinal disease	3 (6.1)	2 (3.9)	0.34
MODS ,n(%)	12 (24.4)	9 (17.6)	0.32

Table No 5 Need and duration of mechanical ventillation and length of PICU stay

Parameters	Vitamin D deficiency group(n=49)	No deficiency group(n=51)	P value
No of patients mechanically ventillated, n(%)	20(40.8%)	16(31.3%)	0.52
Number of days in ventilator, mean±SD	7.5±5.8	5.5±3.1	0.15
Duration of PICU stay (in days), mean±SD	7.5±5.1	5.4±3.2	0.004

Table No 6: Comparison of mortality between the two groups

Mortality rate	Vitamin D deficient group(n=49)		'no deficiency' group (n=51)		P value
	Number	Percentage	Number	Percentage	0.006
	15	30.6	13	25.4	

Discussion

Our study suggests a high prevalence (49%) of vitamin D deficiency in our study population. This was comparable to the study published by Ponnarmeni S et al[16], in which they found the prevalence of VDD in children with sepsis to be 50.8%. Another study conducted in south India by Ebenezer K et al[12] found the percentage of VDD in critically ill children to be 40%. However, in yet another Indian study by J Sankar J et al [17], a much higher prevalence (74%) of vitamin D deficiency was noted among critically sick children. McNally JD et al [10] in their study found the prevalence of VDD among critically ill children to be 69% whereas Madden K et al [9] found it to be 40.1 %.

Such wide variations in the prevalence of VDD in different studies may be due to the indigenous differences in the population studied .Some other factors such as dietary intake, vitamin D supplementation, timing and duration of exposure to sunlight, skin pigmentation and genotype variation in the various proteins involved in vitamin D transportation, functioning and metabolism may be responsible.[18] High incidence in our study may also be due to high incidence of underlying deficiency in the general population. The various other additional factors that may operate in causing low vitamin D level in critically ill children include organ dysfunction, altered metabolism, acute care interventions, transcapillary

leak, fluid administration or any significant hemorrhage.[19]

Few studies have documented significant association of vitamin D deficiency with poor outcomes such as longer duration of ICU stay[10,19], increased requirement of inotropes[11,15] and higher admission illness severity scores [9,10] and death rates, increased rates of ventilator-associated pneumonia, blood culture positivity and an increased incidence of organ dysfunction

Our study revealed a higher illness severity (higher PRISM III SCORE) in VDD group as compared to 'no deficiency' group, and the difference was statistically significant. A few studies found an inverse correlation between VDD and various indices of illness severity[9,10] while others found no such association.[11,15] Madden K et al[9] noted that the median PRISM-III raw score on admission day was 5 (IQR 0–11.5), and it was inversely correlated with 25(OH)D level (r = -0.23, P value <.0001) .In a study conducted by Ebenezer K et al[12] conducted in South India, higher PIM score was found to be associated with low vitamin D levels ($r_s = -0.29$, p v= 0.04). Ponnarmeni S et al16 also found a higher illness severity (higher PRISM III score) in VDD group as compared to no deficiency group (17 (13–22) vs 14 (13–22), p value =0.26).

The current study also revealed that children with VDD had an increased incidence of shock and an increased requirement of catecholamines, although the difference was not statistically significant when compared to the 'no deficiency' group. Madden et al.[9] in their study observed that patients who received vasopressors had lower levels of 25(OH)D than those who did not (median 19.8 vs 24.3 ng/ml, P value= 0.0001) and an increased use of vasopressors was correlated with decreasing 25(OH)D levels (r=-.19, Pv<.0001). An increased incidence of septic shock in VDD group compared to 'no deficiency' group(50.8% vs 49.2%, p value 0.85) was found in the study by Ponnarmeni S et al[16]. Increased requirement of catecholamines was also noted in VDD group both in studies by Sankar J et al [17](53% vs 31%, p value 0.06) and Ponnarmeni S et al [16](49.2% vs 44.3%, p value 0.59).

The requirement of mechanical ventillation, in our study, was higher in VDD group compared to those not deficient (40.8% vs 29.4%, p value 0.52), though the difference was not significant statistically. This is similar to the studies done by Sankar J et al [17](57% vs 39%, p value 0.10) and Ponnarmeni S et al [16] (55.6% vs 42.6%, p value 0.15).

Our study showed a significant difference in the length of PICU stay between Vitamin D deficient and 'no deficiency' group. Vitamin D deficient children had a longer duration of PICU stay (7.5days (5.1)) than non deficient (5.4 days(3.2),p value 0.004).Similarly ,in the study by Sankar J et al[17], the PICU stay was significantly longer in VDD group(7days(2-12) vs 3 days(2-5), p value 0.006).However, no significant effect on length of PICU stay was noted by Ponnarmeni S et al.[16]

Lastly, percentage of mortality was also higher in VDD children than those not deficient(30.6% vs 25.4%, p value 0.006).Similarly, Ponnarmeni S et al [16]also noted a higher mortality in VDD group (15.9% vs 14.7%),though the difference was not statistically significant. The higher mortality percentage in our study might be possibly due to increased illness severity at presentation, late referral from the periphery ,increased prevalence of malnutrition and infections or any gap in health care delivery.

Strength and Limitations

Our current study reveals a high prevalence of vitamin D deficiency in critically ill children and its association with greater illness severity and longer duration of PICU stay. A well defined eligibility criteria and systematically done prospective data collection are the strengths of the study.

The limitations of the study are as follows.

1) The study was done for a very small period of 6 months only.
2) Certain factors which may have a influence on vitamin D levels could not be

investigated: serum phosphorus, alkaline phosphatase and parathyroid hormone.

3) Also, the effect of vitamin D supplementation could not be assessed.

Conclusion

From the present study, we observed a high prevalence of Vitamin D deficiency in critically ill children in our study population. Vitamin D deficiency was found to be associated with greater illness severity, longer duration of PICU stay and higher mortality. Thus, in future, further large scale interventional studies are needed to be undertaken to study the outcomes of vitamin D supplementation in early stages of critical illness.

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