Hypovitaminosis D and Parathyroid Hormone Response in Critically Ill Children with Sepsis: A Case-control Study

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Abstract

Background: Critically ill Indian children have a higher prevalence of vitamin D deficiency. However, there is not much data available on the subgroup with sepsis. It has been reported that there is an impaired response of parathyroid hormone (PTH) to vitamin D deficiency in critically ill children and adults. Hence, we also sought to analyze the PTH response to vitamin D among the subgroup of critically ill children with sepsis.

Patients and methods: Vitamin D and PTH levels of 84 critically ill children with sepsis (cases) and 84 controls were compared between November 2018 and February 2020. Hypovitaminosis D was defined as levels <30 ng/mL.

Results: The median (IQR) of vitamin D for cases was 26 (21.30–29.95) ng/mL and that for controls 39.3 (33.65–50.2) ng/mL; p <0.001. Cases had a higher prevalence of hypovitaminosis D as compared to controls (79.7 vs 9.5%; p <0.001). Among the cases, mortality was 24.6% in the 65 children with hypovitaminosis D and 10.5% in those with sufficient vitamin D; the differences were not statistically significant (p = 0.339). There were no significant differences in the duration of pediatric intensive care unit (PICU) stay, serum calcium, PTH, and disease severity among the aforementioned groups. Out of the 65 children with hypovitaminosis D, only 9 (13.8%) were PTH responders. There were no statistically significant differences in mortality, the PICU stay, or disease severity at admission between PTH responders and nonresponders.

Conclusions: Hypovitaminosis D was more prevalent among critically ill children with sepsis compared to controls. Parathyroid gland response to hypovitaminosis D was impaired in children with sepsis.

Keywords: Calcium, Critically ill children, Parathormone, Vitamin D deficiency.

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Introduction

Vitamin D deficiency is a major public health issue among children throughout the globe. It has been reported that vitamin D deficiency with serum levels <20 ng/mL has a prevalence ranging from 16 to 90% among children the world over.[1]

The importance of vitamin D extends beyond its familiar role in bone mineral metabolism. Low vitamin D levels have been associated in children with a plethora of clinical conditions including obesity, insulin resistance, metabolic syndrome, type 1 diabetes, cystic fibrosis, celiac disease, and asthma.[2] Besides, vitamin D supplementation has been found to be effective in respiratory tract infections like pneumonia, tuberculosis, influenza A, and asthma exacerbations.[3] Studies have reported that children with sepsis have lower vitamin D levels than control participants.[4] It is also known that sepsis is a major cause of pediatric deaths the world over. Mortality ranged from 1 to 5% for sepsis and 9 to 20% for severe sepsis among children globally.[5] In summary, deficiency of vitamin D is an accompaniment with several diseases including sepsis, which is a major cause of pediatric mortality.

The prevalence of vitamin D deficiency varies across different geographic locations. The variations have been attributed to the differences in diet, sunlight exposure, solar zenith angle, skin pigmentation, and ultraviolet index.[6] There are a limited number of studies across different geographical areas of India that have reported varied prevalence of vitamin D deficiency among critically ill children.[7-11] However, not many have focused on the specific subgroup of critically ill children with sepsis.[12] Hence, this study was conducted in a coastal city of South India to assess the vitamin D status of critically ill children with sepsis as compared to that of a control group. There are studies reporting an impaired response of parathyroid hormone (PTH) to vitamin D deficiency among children and adults admitted to the intensive care unit (ICU).[8,13,14] Since there are no similar data among critically ill children with sepsis, we also sought to analyze the PTH response to vitamin D among the subgroup of critically ill children with sepsis.

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Materials and Methods

This was a case-control study conducted between November 2018 and February 2020 at a tertiary care center in Mangaluru, Karnataka, India (latitude of 12.87° N and longitude of 74.88° E at 22 m above the sea level). This public hospital caters to the routine, elective, and emergency medical or surgical needs of children belonging to the surrounding areas. The sample size of 84 cases and 84 controls was calculated with a power of 90 at a 95% confidence level, assuming that 65% of the critically ill children and 40% of control children would have hypovitaminosis D on the basis of relevant data among Indian children.[9,12] Approval was obtained from the institutional ethics committee (IEC). A written informed consent or assent was obtained from the parents of the children after explaining the purpose of the study in their local language. Children aged between 1 month and 18 months admitted to pediatric intensive care unit (PICU) with confirmed or suspected infection with a Pediatric Sequential Organ Failure Assessment (pSOFA) score of two points or more were included as cases. Those who were admitted in the wards without suspected infection and pSOFA score of less than two points were controls. Children known to have previous organ dysfunction, rickets, and chronic kidney disease, on oral supplements of calcium and vitamin D (4 weeks prior to sample collection), were excluded. Baseline data including age, sex, weight, and relevant blood investigations done were recorded. pSOFA used in this study was the adapted and validated pediatric version of the SOFA score for critically ill children.[15] It was developed by modifying the original SOFA score variables for pediatric use. The renal and cardiovascular variables of the SOFA score were modified using age-appropriate cutoff from the Pediatric Logistic Organ Dysfunction 2 scoring. The respiratory scoring was expanded to include the SpO_2-FiO_2 ratio. The pSOFA score was calculated on the first day of admission with the worst value for each of the six variables used to calculate the subscores. If a variable was not recorded, it was assigned a score of 0. pSOFA score obtained was the sum of the six subscores (ranging from 0 to 24 points). In the present study, the preinfection pSOFA score was assumed to be zero. Patients with sepsis were defined as those with confirmed or suspected infection who had a pSOFA score of 2 points or more in the first 24 hours of PICU admission. Three milliliters of plain blood sample was collected aseptically from children who fulfilled the inclusion criteria at the earliest before 24 hours of admission. Serum was separated and stored in plain vacutainer tubes at −20°C. Once an adequate number of samples were collected to run the test, vitamin D and PTH levels were estimated using the enzyme-linked immunosorbent assay (ELISA) technique. The Calbiotech, Inc. 25-hydroxy (25-OH) vitamin D ELISA (catalog no. VD220B Calbiotech Inc., Spring Valley, California, United States) and Biomerica Intact-PTH ELISA (catalog no. 7022; Biomerica Inc., Irvine, California, United States) were used for measuring the serum concentrations. "Total 25-hydroxy (25-OH) Vitamin D," the sum of 25-hydroxy (25-OH) vitamin D2, and 25-hydroxy (25-OH) vitamin D3 were measured using the kit. The vitamin D values were subcategorized as deficiency (<20 ng/mL), insufficiency (20–29.9 ng/mL), and sufficiency (≥30 ng/mL) as in the previous studies.[7,9,14] Hypovitaminosis D was defined as vitamin D levels <30 ng/ mL. Hypocalcemia was defined as serum calcium (corrected for albumin) <8.5 mg/dL. Based on PTH response, children with either hypocalcemia or hypovitaminosis D were classified as PTH responders or PTH nonresponders. PTH responders were needed to have PTH >65 pg/mL together with hypovitaminosis D and/or hypocalcemia as in a previous study.[8]

The primary outcome measure was to compare serum 25(OH) D levels between critically ill children with sepsis and the control group of children. Among the cases (critically ill children with sepsis), we compared subgroups with hypovitaminosis D and without hypovitaminosis (vitamin D sufficient) with respect to mortality, disease severity, and duration of ICU stay. Similarly, among the cases with hypovitaminosis D, the PTH responder subgroup was compared with the group without adequate PTH response with respect to clinical outcomes.

Data entry and statistical analysis were performed using SPSS Statistics for Windows, version 16.0 (SPSS Inc., Chicago, Illinois, United States). Non-normally distributed continuous variables were summarized using median with interquartile ranges. Demographic variables were recorded as percentages or medians and interquartile ranges (IQR). Serum calcium, 25(OH)D levels, and PTH levels were compared using Mann–Whitney *U* test. Vitamin D status of cases and controls was compared using chi-square or Fisher's exact test, as appropriate. The correlation between vitamin D and PTH for both the groups was compared using Pearson's correlation. For comparing the length of PICU stay among cases with or without hypovitaminosis D, Mann–Whitney *U* test was applied. The normality of the data was checked by Shapiro-Wilk test. All tests were two-tailed, and $p < 0.05$ was taken as significant.

Results

A total of 168 children were included in the study, out of which 84 were cases admitted to the PICU with sepsis and 84 were controls admitted towards with no sepsis (for noninfective conditions). The group of children admitted to PICU was for acute respiratory infections (38.1%), central nervous system infections (21.4%), dengue (11.9%), gastrointestinal infections (11.9%), and other infectious conditions like malaria, typhoid, tuberculosis, and HIV (16.6%). The children in the control group were mostly admitted for elective surgical conditions.

Table 1 compares the baseline demographic and laboratory parameters of critically ill children with sepsis and controls. The children with sepsis, admitted to PICU, were significantly

Table 1: Comparison of the baseline demographic and laboratory parameters among the two groups of children

Variables	*Children with sepsis (cases), median (IQR)*	*Children without sepsis (controls), median (IQR)*	*p**
Age (months)	18 (6–66)	72 (30–117)	<0.001
Weight (kg)	9.45 (6.52–15.6)	17 (12–25)	<0.001
Hb (gm/dL)	9.85 (8.9–11.6)	11.75 (10.33–12.7)	<0.001
Total count (cells/mm^3)	11,900 (7,425–15,800)	9,600 (4,600–8,400)	0.006
Platelet (lakhs/mm^3)	1.2 (0.8–3.3)	3.2 (2.6–4.16)	<0.001
S. albumin (gm/dL)	3.6 (3–4.2)	4.2 (3.6–4.4)	<0.001
S. creatinine (mg/dL)	0.4 (0.2–0.5)	0.4 (0.2–0.5)	0.66

*Mann-Whitney *U* test

younger than controls who were admitted predominantly for various elective surgical procedures. Hence, the weight of the sepsis group of children was expectedly correspondingly lower. Children admitted to PICU with sepsis consisted of 50 (59.5%) of males. The control group consisted of 41 (48.8%) males. There were no significant differences in the gender distribution of children across groups ($p = 0.163$). Children with sepsis (cases) had lower hemoglobin, lower platelets, and lower serum albumin with higher total counts implying the greater severity of illness among cases compared to controls. Among the children with sepsis, 37 (44%) required inotropes, 72 (85.7%) required oxygen, and 18 (21.4%) expired, whereas the control group children did not need such interventions.

Table 2 shows that the children admitted with sepsis in PICU had lower vitamin D levels compared to the children admitted to wards (control group). The median value of vitamin D for children with sepsis (26 ng/mL) was in the range of hypovitaminosis D (<30 ng/mL), whereas that for controls (39.3 ng/mL) was in the range of vitamin D sufficiency with the difference being statistically significant by Mann–Whitney test (p <0.001). There were no significant differences in the serum calcium (corrected for albumin) and serum PTH levels.

The children were divided into deficiency, insufficiency, and sufficiency based on the vitamin D levels; 69 children with sepsis had hypovitaminosis D compared to 8 in the control group. The difference between groups was statistically significant (p <0.001).

Among both the subgroups of children (cases and controls), there was no correlation observed between PTH levels and vitamin D levels (cases: correlation coefficient 0.048, $p = 0.663$; controls: correlation coefficient −0.008; $p = 0.945$). There was no correlation between serum levels of vitamin D and corrected calcium (cases: correlation coefficient 0.132, $p = 0.255$; controls: correlation coefficient .125, $p = 0.274$.) There was no correlation between serum levels of PTH and corrected calcium as well (cases: correlation coefficient .041, $p = 0.728$; controls: correlation coefficient −0.104, $p = 0.362$.)

Eighty-four children in the group with sepsis admitted to PICU were divided based on vitamin D status into those with hypovitaminosis D (vitamin D <30 ng/mL) and those with vitamin D sufficiency. Table 3 shows the differences between these groups across several parameters. Though the mortality was 24.6% among the 65 children with hypovitaminosis D and 10.5% among the 19 children with sufficient vitamin D, the differences were not statistically significant ($p = 0.339$). There were also no statistically significant differences in the duration of PICU stay, pSOFA score, corrected serum calcium, PTH, oxygen requirement at admission, and need for inotropes among these groups.

Sixty-five children with sepsis admitted to PICU had hypovitaminosis D. Among these children, 9 (13.8%) were PTH responders and 56 (86.2%) were PTH nonresponders. One child among the nine children with secondary hyperparathyroidism expired, whereas the mortality was 26.8% ($n = 15$) among the parathyroid nonresponders. These differences were not statistically significant ($p = 0.433$). There were no statistically significant differences in the PICU stay or disease severity at admission as per pSOFA scores among PTH responders versus nonresponders [PICU stay 2 (2–8.5) days vs 3 (2–9.5) days; $p = 0.634$, and pSOFA scores 4 (2–6) vs 4 (3–6.75); $p = 0.677$.]

Table 2: Calcium, vitamin D, and PTH among the groups

Parameter	*Children with sepsis—Cases*	*Children without sepsis—Controls*
#Calcium (mg/dL) Median (IQR)	9.75 (8.75–9.9)	9.76 (8.9–9.82)
Vitamin D (ng/mL) Median (IQR)	26 (21.30–29.95)	39.3 (33.65–50.2)
PTH (pg/mL) Median (IQR)	30.1 (18.05–44.4)	27.7 (17.7–41.25)
Vitamin D status, n (%)		
Deficiency, 0–20 (ng/mL)	17 (20.2)	0
Insufficiency, 21–29.9 (ng/mL)	48 (57.1)	8 (9.5)
Sufficiency, >30 (ng/mL)	19 (22.6)	76 (90.5)

#Corrected for albumin

Discussion

The present study reports the vitamin D and PTH status of a group of critically ill children with sepsis in comparison with a control group without any acute illness or sepsis. In the present study, we used vitamin D levels <30 ng/mL to define hypovitaminosis D. Normally, vitamin D and PTH levels are inversely correlated up to a certain level of vitamin D after which PTH levels plateau. The transition of the vitamin D-PTH relationship from linear to plateau was at 30 ng/mL in a recent study among Turkish children and hence was suggested as the clinical threshold.[16] Besides, vitamin D level >30 ng/mL suggests sufficiency of vitamin D.[7,9,14]

The prevalence of hypovitaminosis D (<30 ng/dL) among critically ill children was 77.4% comparable to 57.5 to 92.2% reported in previous studies.[7,8,12] The prevalence of vitamin D

Table 3: Comparison of various parameters between septic children with hypovitaminosis D and vitamin D sufficiency

Parameters	*Children with sepsis with hypovitaminosis D (<30 ng/mL), n = 65*	*Children with sepsis with vitamin D sufficiency (>30 ng/mL), n = 19*	*p*
PICU stay, median (IQR) (days)	3 (3–10)	4 (2–10)	0.710*
pSOFA score, median (IQR)	4 (4–8)	3 (3–5)	0.108*
Corrected serum calcium, median (IQR) (mg/dL)	9.76 (8.7–9.93)	9.6 (8.8–9.84)	0.710*
Parathyroid hormone, median (IQR) (pg/mL)	30.1 (19.25–45.7)	27.6 (20.1–47.9)	0.665*
Oxygen requirement at admission (%)	86.2	84.2	1#
Need for inotropes (%)	47.7	31.6	0.213#
Mortality (%)	24.6	10.5	0.339#

*Mann-Whitney *U* test; #Chi-square test

levels <20 ng/mL (deficiency) was only 20.2% among critically ill children, and the deficiency status was not observed in any of the control group children. Hence, we report a lower prevalence of vitamin D deficiency compared to several previous studies where it ranged from 37.9 to 83% among critically ill children.[7–12,17,18] It is interesting to note that among the Indian studies, South Indian studies have reported lower prevalence of vitamin D deficiency among critically ill children with range 37.9 to 40.3% compared to studies from North India with range 50.8 to 83%.[7–12] A study from Kerala with similar food habits (fish in diet) and geographically close to the region of the present study has reported a low prevalence of vitamin D deficiency among children.[19] It has been reported that the 25(OH)D levels in South Indian subjects are relatively higher compared with the subjects from North India, and there is a strong inverse correlation between the 25(OH)D levels and latitude.[20] Hence, the lower prevalence of vitamin D deficiency in children with sepsis in the present study compared to other studies could be due to dietary differences, geographical differences of altitude and latitude,[6,20] in addition to the differences in the underlying disease conditions, methods of estimation of vitamin D,[4] the criteria for PICU admissions, and study settings.

The median value of vitamin D for critically ill children with sepsis (26 ng/mL) was significantly lower than that for controls (39.3 ng/mL). The mean levels for critically ill Indian children ranged from 5.8 to 25.6 ng/mL in various studies.[7,8,10–12] Nearly, 79.7% of the critically ill children with sepsis had hypovitaminosis D (vitamin D levels <30 ng/mL) as compared to the 9.5% in the control group. And 90.5% of children in the control group were vitamin D sufficient. Our findings are in agreement with previous studies that have reported an increased prevalence of vitamin D deficiency among critically ill children with sepsis as compared to controls.[12,17] Hence, our study concurs with the large body of evidence supporting a significant association between vitamin D deficiency or lower 25(OH)D level and sepsis in children.[4]

Among the critically ill children with sepsis, 24.6% of children with hypovitaminosis D expired as compared to 10.5% of children with sufficient vitamin D levels. However, the differences in mortality were not statistically significant. Several previous studies have reported that there was no association between mortality and lower vitamin D levels among critically ill children in line with our findings.[9,10,12,18] The duration of ICU stay was also not affected by vitamin D deficiency status like in the few previous studies.[8,12] There was no association between various parameters indicating illness severity and the vitamin D status of children with sepsis as in earlier reports.[8,12,18]

There was no correlation observed between serum PTH levels and vitamin D levels; serum levels of vitamin D and corrected calcium; and serum levels of PTH and corrected calcium as well for both cases and controls. Similar observations have been reported in critically ill children and adults.[8,13] However, another study reported negative correlation between vitamin D and PTH levels among critically ill adults.[14]

Only 13.8% of the 65 critically ill children with hypovitaminosis D (<30 ng/mL) showed PTH response in the present study comparable to 19.5% reported in a previous study on critically ill children.[8] PTH response was found among 32.5 to 59.5% critically ill adults with vitamin D deficiency (levels <20 ng/mL) in earlier studies.[13,14] The reason for poor response of parathormone to hypovitaminosis D in our study and another study with critically ill pediatric subjects[8] compared to similar adult studies[13,14] has no specific explanation. However, it could be due to the higher levels of vitamin D among our study subjects, different methods of estimation of vitamin D and PTH, and different definitions for PTH response besides age-specific physiologic differences. The presence of underlying malnutrition may have also contributed to the blunted PTH response.

There were no statistically significant differences between PTH responder and nonresponder subgroups of the critically ill children with sepsis and hypovitaminosis D with respect to mortality, PICU stay, and disease severity at admission. Our findings concur with earlier studies in pediatric and adult subjects that found no differences in the mortality among vitamin D-deficient patients with adequate PTH response as compared to PTH nonresponders.[8,13] However, few studies reported increased disease severity among hypovitaminosis D patients with adequate PTH response that is not in agreement with our findings.[8,13,14] The differences in the results could be due to the differences among study subjects, settings in addition to the relatively higher levels of vitamin D among our participants.

Our study had some limitations. The sample size of the study population could have been larger for better the analysis of the data among the various subgroups. Sepsis was defined by clinical parameters, and confirmation of sepsis was not done among included cases. The analysis of PTH response to hypovitaminosis D presented in this study should be viewed in light of the small sample size. Besides, the results of the study cannot be generalized as it is a single-center study with subjects being critically ill children with sepsis. There were significant differences in the median ages of cases and controls. However, there are no different cutoff values to define the adequacy of vitamin D levels in various pediatric age-groups. Thus, these differences would not have affected the results of the study. Serial estimation of vitamin D values at different points during the stay in the hospital could have been more informative.

Conclusion

In conclusion, hypovitaminosis D was more common among critically ill children with sepsis compared to controls. The majority of the critically ill children with sepsis has a blunted parathyroid gland response to hypovitaminosis D. Our findings need to be seen in light of the fact that there was an overall lower prevalence of vitamin D deficiency in the subjects of the present study as compared to previous reports.

Highlights

A higher prevalence of hypovitaminosis D among critically ill children has been reported. We report the same in the focused subset of critically ill children with sepsis. The majority of critically ill children with sepsis has a blunted parathyroid gland response to low vitamin D levels.

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