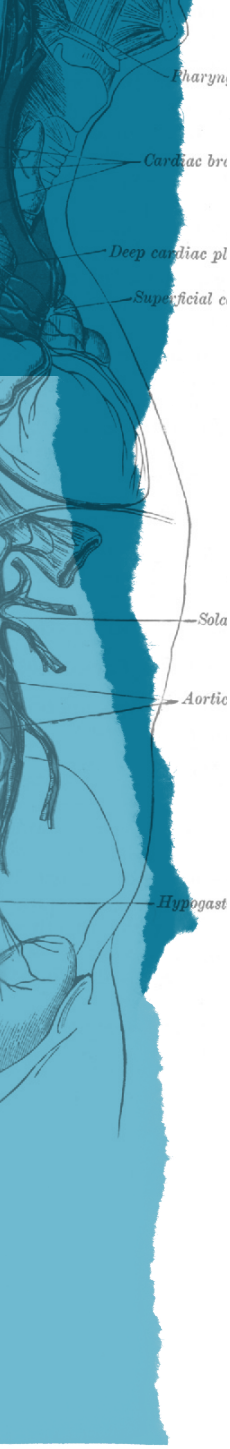

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Vitamin D Status and Disease Severity in Critically Ill Pediatric Patients

Estado de Vitamina D y gravedad de la enfermedad en pacientes pediátricos críticamente enfermos

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ABSTRACT

Objectives: The objective of this study was to evaluate Vitamin D (VD) status and its association with disease severity in critically ill pediatric patients.

Methods: An observational follow-up study was conducted on a prospective cohort of pediatric patients admitted to the intensive care units (ICU) of two health institutions. All admitted patients underwent measurement of 25-OH-VD, which were categorized as deficiency, insufficiency, or normal. The outcome variables were mechanical ventilation, the need for inotropes, renal replacement therapy, and mortality.

Results: One-hundred seventy-five pediatric patients were followed up. The mean VD was (25.43 mg/dl, SD = 10.17). The prevalence of deficiency was 26.29 % (n= 46), and for insufficiency, 48 %. Patients with VD deficiency (adjusted RR 2.07 CI95 1.12 – 3.82) had a higher risk of requiring inotropes.

Conclusion: VD deficiency was associated with the need for inotropic medication during ICU stay.

Keywords: Deficiency, insufficiency, vitamin D, Pediatric Critical Care.

RESUMEN

Objetivo: El objetivo de este estudio fue evaluar el estado de la vitamina D (VD) y su asociación con la gravedad de los pacientes pediátricos críticamente enfermos.

Metodología: Se llevó a cabo un estudio observacional de seguimiento en una cohorte prospectiva de pacientes pediátricos admitidos en los servicios de UCI en dos instituciones de salud. Todos los pacientes admitidos tuvieron una medición de los niveles de 25-OH-Vitamina D, y se categorizaron como "deficiencia", "insuficiencia" y "normal". Las variables de resultados fueron ventilación mecánica, necesidad de inotrópicos, terapia de reemplazo renal y mortalidad.

Resultados: Ciento setenta y cinco pacientes estuvieron bajo seguimiento. La media de vitamina D fue (25.43 mg/dl, DE = 10.17). La prevalencia de deficiencia fue de 26.29 % (n= 46) e insuficiencia 48 %. Pacientes con VD deficiente (ajustado RR 2.07 CI95 1.12 - 3.82) tuvieron mayor riesgo de requerir inotrópicos.

Conclusión: La deficiencia de VD fue asociada con la necesidad de usar inotrópicos durante la estancia en UCI.

Palabras clave: Deficiencia, insuficiencia, vitamina D, cuidado crítico pediátrico.

INTRODUCTION

Vitamin D (VD) is a prohormone that plays a key role in humans, since it has to do with the balance of calcium, phosphorus, and bone structure[1]. VD deficiency has negative effects on body composition, bone metabolism[2], cardiovascular, neurological, and respiratory systems; and the immune response[3]. Various studies have shown an association between lower VD levels and diseases such as asthma, multiple sclerosis, glucose intolerance, diabetes, arterial hypertension, acute respiratory infection, obesity, cancer, and cardiovascular diseases[4–6].

It is estimated that nearly one billion people worldwide have VD deficiency or insufficiency[7], representing a global public health problem, even in countries with adequate sun exposure through-

out the year[8]. In the pediatric population, the prevalence of VD deficiency is between 31.4 % and 45.6 %[9], and can reach 55 % in critically ill patients[10].

In critically ill pediatric patients, VD deficiency and insufficiency have been associated with greater disease severity[10], the need for ICU interventions, the need for ventilator support, vasoactive agents, and the risk of sepsis[11–14]. Additionally, it has been shown that VD deficiency during ICU stay increases the risk of dying by up to two times, compared to pediatric patients with normal VD levels[15,16].

In Latin America, only one study has been conducted, in Chile, by Bustos et al. (2016). It showed an association between VD deficiency with the use of vasoactive drugs (RR 1.6; 95 % CI 1.2 – 2.3), mechanical ventilation (RR 2.2; 95 % CI 1.2 - 3.9), septic shock (RR 1.9; 95 % CI 1.3 - 2.9), and need for resuscitation fluids in the first 24 hours (RR 1.5; 95 % CI 1.1 - 2.1) [17]. In Colombia, the prevalence of VD deficiency or insufficiency in pediatric patients admitted to intensive care units, and its association with disease severity, are unknown. The objective of this study was to evaluate the VD status and its association with adverse clinical outcomes in critically ill pediatric patients.

MATERIALS AND METHODS

Design

An observational follow-up study was conducted on a prospective cohort of pediatric patients admitted to the intensive care units (ICU) of two health institutions, between August 2021 and February 2022. The two participating health institutions were highly complex, and they care for patients from all socioeconomic strata in the southern region of Colombia. All admitted patients had their 25-OH-VD levels measured and were under followed-up until discharge from the ICU.

Participants

Pediatric patients between one-month old and 18 years, admitted to the pediatric ICU for medical or surgical reasons, and whose parents or legal guardian had signed the informed consent form. Patients with renal, hepatic or parathyroid endocrine disease (hyper/hypoparathyroidism) prior to ICU admission, with proven malabsorptive status, were excluded. Patients with known VD resistance or VD supplementation three months prior to admission were also excluded. The

selection of the participants was carried out consecutively by including all the patients who met the inclusion criteria between August 2021 and February 2022.

Sample Size

The sample size calculation was carried out considering the prevalence of VD deficiency reported in the literature to be 54.8 %[10], with a confidence level of 95 %, and an accuracy of 7.4 %, obtaining a sample size of 175 patients.

Variables

The exposure variable was VD level, which conformed three cohorts. Deficiency with a 25-OH-VD concentration less than 20 ng/ml; insufficiency, less than 30ng/ml; and normal VD levels, equal to or more than 30ng/ml. The outcome variable was disease severity, which included mortality, the need for mechanical ventilation, inotropes and renal replacement therapy in the ICU. The independent variables were sex, age, medical diagnosis, PRISM scale score, PELOD scale, and nutritional status, which was evaluated for children under and over 5 years of age. Paraclinical variables including phosphorus, calcium, and blood count, were also evaluated.

Data Source

A biological sample of VD (25-OH-VD) was collected on the date of admission to the ICU, through phlebotomy and extraction of 2 ml of blood, following the institutional protocol. The samples were protected from sunlight, centrifuged, and refrigerated. The analysis was performed using a Roche electrochemiluminescence immunoassay. The collection, processing, and analysis procedures were similar between the two institutions where the patients were recruited. Information on paraclinical tests, medical diagnosis, and nutritional status was collected during the first 24 hours of admission to the unit. Outcomes were identified every day through medical assessments, until the patient was discharged from the ICU.

Statistical Analysis

Categorical variables were analyzed using absolute and relative frequencies, whereas quantitative variables were described using measures of central tendency (median) and dispersion (interquartile range). The Wilcoxon rank test was used to identify significant difference in the level of VD,

according to the occurrence of the evaluated outcomes. To calculate adjusted relative risk (95 % of confidence), four models of log-binomial regression were constructed for each outcome (mortality, mechanical ventilation, use of inotropes, and renal replacement therapy). Independent variables were deficient, insufficient, or suboptimal levels of VD, with covariables including age and severity of illness using the PRISM scale. These covariables were chosen based on clinical criteria. Due to convergence methods that might emerge with log-binomial regression, for this study, a generalized lineal model with binomial family (link="log") was used. Statistical analysis was performed using the RStudio 3.4 program.

Ethical Issues

The study was approved by the ethics committee of both institutions. In addition, all participants were aware of the informed consent process. Ethical principles of beneficence, non-maleficence, justification, and autonomy were applied.

RESULTS

Clinical Aspects

During the study period, 175 pediatric patients admitted to the ICU from two health institutions were followed-up. 107 of them were male. Half of the patients were 48 months old (table 1).

Forty-eight percent of patients under 5 years of age had a normal weight-for-age. The prevalence of acute underweight (risk, moderate, and/or severe) was 44.44 % (table 1). In patients older than 5 years, 3 of every five patients had a normal weight (58.97 %), and the prevalence of overweight or obesity in patients older than 5 years was 15.37 % (table 1).

Table 1. Sociodemographic variables of pediatric patients admitted to the Intensive Care Unit in two health institutions

Data	Total N= 175
Age (months)	
Median (IR)	48 (11.50 – 119.50)
Mean (SD)	70.28 (63.96)
Age groups	
Minor infant	44 (25.14)
Older infant	13 (7.43)
Preschool	45 (25.71)
School	34 (18.43)
Adolescents	39 (22.29)
Sex	
Female	68 (38.86)
Male	107 (61.14)
Stratum	
Low – low	135 (77.14)
Low	35 (20.00)
Middle – low	5 (2.86)
Nutritional status < 5 years	
Normal	48 (48.5)
Acute underweight risk	21 (21.2)
Moderate acute underweight	10 (10.1)
Acute severe underweight	13 (13.1)
Overweight risk	4 (4.0)
Overweight	3 (3.0)
Nutritional status > 5 years	
Normal	46 (59.0)
Thinness risk	11 (14.1)
Thinness	9 (11.5)
Overweight	4 (5.1)
Obesity	8 (10.2)

Note. IR: Interquartile range; S.D: Standard deviation.
Source: own elaboration.

Regarding the phosphorus, calcium, and hematology parameters, no major alterations were observed (table 2). Half of the patients had a comorbidity of clinical importance, with neurological disease being the most frequent (18.29 %), and one out of every 10 patients had oncological

disease (table 3). Patients admitted to the pediatric ICU had average PRISM and PELOD values of 7.0 and 3.0, respectively. The average number of days of mechanical ventilation and ICU stay were 6.60 and 5.0 days respectively (table 3).

Table 2. Level of phosphorus, calcium, leukocytes, neutrophils, lymphocytes, eosinophils, monocytes, hemoglobin and platelets in pediatric patients admitted to the ICU in two health institutions

Data	Total N= 175
Phosphorus	
Median (IR)	4.10 (3.5 – 5.1)
Mean (SD)	4.39 (1.65)
Calcium	
Median (IR)	1,3 (1,15 – 9,1)
Mean (SD)	4.56 (4.07)
Leukocytes	
Median (IR)	11850 (6875 – 17815)
Mean (SD)	14661 (19275.8)
Neutrophil	
Median (IR)	6860 (3345 – 12010)
Mean (SD)	8617.97 (6936.17)
Lymphocytes	
Median (IR)	2230 (1375 – 4190)
Mean (SD)	4304.46 (12403.89)
Eosinophils	
Median (IR)	50.0 (10.0 – 210.0)
Mean (SD)	244.8 (874.22)
Monocytes	
Median (IR)	570 (330 – 1000)
Mean (SD)	750.88 (666.27)
Hemoglobin	
Median (IR)	11.29 (9.7 – 12.60)
Mean (SD)	11.09 (2.29)
Platelets	
Median (ir)	336000 (216500 – 432000)
Mean (sd)	333548.6 (183357.4)

Note. IR: Interquartile range; S D: Standard deviation.
Source: own elaboration.

Table 3. PRISM, PELOD, ICU stay, days on MV and inotropic index in pediatric patients admitted to the ICU in two health institutions

Data	Total N= 175
Comorbility	
Neurological	32 (18.29)
Oncological	17 (9.71)
Cardiac	8 (4.57)
Respiratory	8 (4.57)
Gastrointestinal	6 (3.43)
Metabolic	6 (3.43)
Prism	
Median (ir)	7.0 (4.0 – 10.0)
Mean (sd)	6.78 (4.97)
Pelod	
Median (ir)	3.0 (2.0 – 4.0)
Mean (sd)	3.25 (3.50)
ICU stay	
Median (ir)	5.0 (3.0 – 10.0)
Mean (sd)	7.72 (7.44)
Days of mv	
Mean (sd)	6.60 (7.31)
Inotropic index	
Mean (sd)	8.39 (26.26)

Note. IR: Interquartile range; SD: Standard deviation; MV: Mechanical ventilation. ICU: Intensive Care Unit.
Source: own elaboration.

Vitamin D Levels

The average VD was 25.43 mg/dl (SD = 10.17). The prevalence of alterations in the VD levels was 74.29 %. Of all patients, 46 (26.29 %) had VD deficiency, and 48 % had insufficiency.

Outcomes

Mechanical ventilation was the most frequent, with an incidence of 21.71 %, followed by the use of inotropes with 20.57 % (table 4). Patients with VD deficiency or low values had a significantly higher risk of requiring inotropes during their ICU stay (table 4). No association was observed

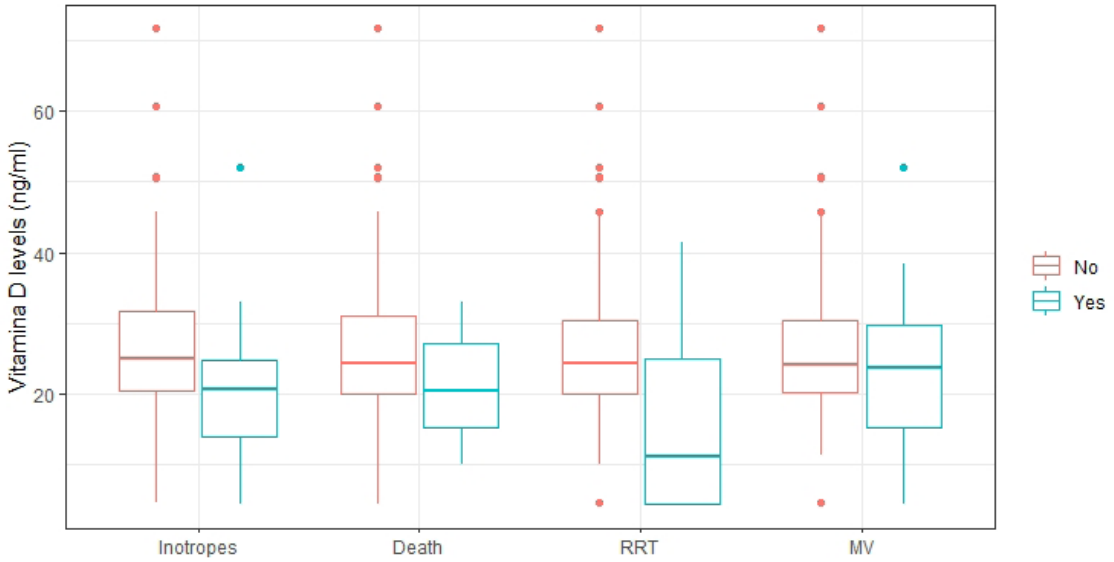
between VD levels and requirement for mechanical ventilation, renal replacement therapy, or in-hospital mortality (table 4).

Table 4. Association between vitamin D levels with mechanical ventilation, use of inotropes, RRT and mortality in pediatric patients admitted to the ICU in two health institutions

Data	MV N= 39 (21.71%)	p	Crude RR (CI95%)	Adjusted RR (CI95%)*
Vitamin D levels				
Deficiency	15 (32.61)	0.06	1.75 (1.01 – 3.04)	1.56 (0.84 – 2.91)
Insufficiency	15 (17.86)	0.81	0.89 (0.42 – 1.88)	0.83 (0.39 – 1.78)
Alteration	30 (23.08)	0.83	1.15 (0.59 – 0.84)	1.56 (0.84 – 2.91)
Data	***Inotropes N= 58 (20.57%)***			
Vitamin D levels				
Deficiency	17 (36.96)	<0.01	2.51 (1.43 – 4.40)	2.07 (1.12 – 3.82)
Insufficiency	16 (19.05)	0.07	2.86 (0.88 – 9.29)	2.57 (0.83 – 7.97)
Alteration	33 (25.38)	<0.01	3.81 (1.23 – 11.81)	2.07 (1.12 – 3.82)
Data	***Death N= 10 (5.71%)***			
Vitamin D levels				
Deficiency	5 (10.87)	0.13	2.80 (0.85 – 9.25)	2.33 (0.68 – 8.01)
Insufficiency	4 (4.76)	0.66	2.14 (0.25 – 18.60)	1.68 (0.17 – 16.93)
Alteration	9 (6.92)	0.46	3.11 (0.41 – 23.91)	2.34 (0.68 – 8.01)
Data	***RRT N= 6 (3.43%)***			
Vitamin D levels				
Deficiency	4 (8.70)	0.04	5.61 (1.06 – 29.61)	4.02 (0.73 – 21.98)
Insufficiency	1 (1.19)	1.0	0.54 (0.03 – 8.36)	0.45 (0.02 – 7.55)
Alteration	5 (3.85)	1.0	1.73 (0.21 – 14.42)	4.02 (0.73 – 21.98)

Note. * Adjusted RR by age and PRISM scale; MV: Need of mechanical ventilation; RRT: Renal replacement therapy; RR: Relative risk; CI: Confidence intervals.
Source: own elaboration.

VD levels were lower in patients who required inotropes (median 24.91 versus 20.72, p<0.01), renal replacement therapy (median 24.32 versus 11.10, p=0.08), and in deceased patients (median 24.32 versus 24.35, p = 0.15) (figure).



Note. MV: Mechanical ventilation; RRT: Renal replacement therapy; Blue bar: Yes; Red bar: No.

Figure. Vitamin D level in critically ill patients according to inotropic requirement, renal replacement therapy, mechanical ventilation, or death

DISCUSSION

This is the first published cohort study carried out in Colombia, and one with the largest sample size in Latin America. It evaluated VD deficiency and insufficiency, and their association with disease severity in critically ill pediatric patients. The study found that critically ill pediatric patients have decreased levels of VD. Additionally, patients with VD deficiency had a higher risk of requiring inotropes during their stay in the ICU.

The results are consistent with preliminary reports. In patients admitted to pediatric ICU, studies have found VD deficiency between 40 % and 80 % of patients[18–21], with an average VD less than 25 ng/ml[7]. Although it is unknown if this subnormal level of VD is due to the critical condition of the patient, as it has been found that critically ill patients have lower levels compared to healthy-pa-

tient controls[20,22]. Therefore, it is necessary to assess the level of VD in critically ill patients, since it has been shown that acute decrease could even be more dangerous than chronic deficiency[3].

Studies in the critically ill adult population have shown an association between the level of DV and disease severity. In this regard, VD deficiency represents a risk for clinical outcomes such as the need for mechanical ventilation, longer hospital stay[23], sepsis, in-hospital mortality[24], and vasoactive requirement[3]. On the other hand, in the pediatric population, the studies have not been conclusive due to the high heterogeneity in the methodology and in their results. However, cardiovascular support has been one of the most found severe outcomes[3].

This study found that suboptimal levels and VD deficiency increased the risk of needing inotropes, similar to the study report by Bustos et al[17]. This could be related to the behavior of VD that influences the structure and function of myocytes[25], and the functioning of the respiratory system[3]. In this regard, analytical studies with a larger sample size are needed to analyze the association between VD and disease severity. Additionally, clinical trials are needed to evaluate the effect and safety of VD supplementation in critically ill pediatric patients.

This study has some limitations that should be taken into account. The first is the lack of knowledge of each patient's VD level prior to admission to the ICU, so it is not possible to assure that the deficiency is acute or chronic. As a second limitation, in this study, the change in the level of VD during the ICU stay was not evaluated, we report an information bias that could influence the disease severity. Thirdly, despite finding a significant association between deficiency and the need for inotropes, it is necessary to assess other criteria to establish causality, since these are multiple-risk factor patients. Finally, a selection bias is reported in this study, because it was conduct in only two health institutions, therefore results cannot be generalizable to all pediatric critically ill patients.

CONCLUSIONS

Pediatric patients on admission to the ICU have decreased levels of VD. Critically ill pediatric patients with VD deficiency are at greater risk of requiring inotropes during their stay.

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Conflict of interest statement: Authors declare no conflict of interests.

Contribution of each author: DGS and IJA designed the entire protocol and were the head of the study. DGS, IJAG, DCD, and PPL participated in the data collection and the elaboration of the manuscript. JARC analyzed the data and participated in the elaboration and critical review manuscript. All authors contributed to the article.

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