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Impact of a Nutrition Protocol on Vitamin D Supplementation in a Pediatric Intensive Care Unit: A Retrospective Cohort Study

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Abstract

Background: Vitamin D deficiency (VDD) is highly prevalent in pediatric critically ill patients and is a potentially modifiable risk factor during critical illness. There are no established national or international recommendations for vitamin D supplementation in Pediatric Intensive Care Unit (PICU) patients. **Objectives:** This monocentric study aims to compare the practices regarding Vitamin D supplementation before and after the introduction of a nutrition protocol (NP). **Methods:** We retrospectively analyzed vitamin D administration (time from PICU admission to initiation, amount of supplementation, accordance with existing guidelines) in children aged from 0 to 16 who were admitted to the PICU of Lausanne University Hospital for more than 48 hours the year before and after the introduction of a NP. **Results:** Vitamin D supplementation increased after NP introduction (95 IU per day more, ($p < 0.0001$). More patients received vitamin D during their stay (95% after vs. 77% before, ($p < 0.0001$). The dose followed NP recommendations for children under 12, it was higher for older children. According to Swiss guidelines for the general pediatric population, vitamin D supplementation was accurate in children under one year old before and after NP implementation. However, it was less than recommended for patients over one year old. **Conclusions:** The implementation of a NP significantly enhanced the scope of vitamin D supplementation. This study also highlights the practical limitations in meeting the recommended requirements with certain galenic formulations.

Keywords: vitamin D deficiency; vitamin D supplementation; nutrition protocol; Pediatric Intensive Care Unit

1. Introduction

Vitamin D is crucial in calcium-phosphate metabolism, bone mineralization, and many metabolic pathways modulating the immune system, cellular growth, and differentiation [1-5]. Vitamin D has a dual origin: photosynthesis in the skin during UVB irradiation by sunlight and dietary sources. Although standards vary worldwide, a 25(OH)D serum level of 50 nmol/l is widely used as the threshold to define Vitamin D deficiency (VDD), with 25 or 30 nmol/l representing severe deficiency. These thresholds specifically apply to bone health, and severe deficiency should be avoided at all ages to prevent rickets and osteomalacia [5]. According to some criteria and considering the evidence on both skeletal and pleiotropic vitamin D effects, serum levels of 25(OH)D should be >75 nmol/l, which would mean that most people worldwide could be considered to have vitamin D 'insufficiency' [6,7].

Approaches to improve vitamin D status in the population include increasing UV-B exposure, consuming vitamin D-containing food, food fortification, vitamin D supplements, and weight loss [2,3]. Historically, a daily vitamin D intake of 400 International Units (IU) was recommended because

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this approximates the vitamin D content of one teaspoon of cod liver oil, which was observed to be sufficient to prevent rickets. Currently, many guidelines exist with different recommended daily doses of vitamin D for the general population. They rely on the results of studies that link thresholds of serum concentrations of 25(OH)D with musculoskeletal or extraskeletal outcomes. *Roger Bouillon* reviewed the vitamin D guidelines from more than 40 countries. These different guidelines agree that children under one year of age require a daily vitamin D supplement, with an average recommended dose of 400 IU. This recommendation often extends to children aged 1–3 years and to all children or adults with insufficient exposure to sunlight, with suggested doses ranging from 100 to 2000 IU/day [8]. In 2012, the Swiss Federal Office of Public Health (FOPH) made recommendations, revised in 2016, to achieve a 25(OH)D serum level of >50 nmol/L in 97% of the population, focusing on bone health only. The recommended doses for children are 400 IU/day for infants up to 1 year and 600 IU/day from the second birthday for risk groups only [9,10]. Since 2012, the Swiss Society of Pediatrics (SSP) has also recommended administering 400 IU/day of vitamin D from the second week of life throughout the first year. They have made no recommendation for older children [11].

In pediatric critically ill patients, VDD at admission is highly prevalent around the globe, with rates ranging from 25% to 84% [5]. Pediatric Intensive Care Unit (PICU) patients are more prone to hypovitaminosis D than the general pediatric population because of reduced endogenous production, restricted dietary intake, stress situations with increased vitamin D tissue consumption, decreased hepatic and renal hydroxylation, malabsorption, and critical illness-related interventions. VDD has been associated with increased mortality, illness severity, need for vasoactive agents, mechanical ventilation and infection. Therefore, VDD could represent a potentially modifiable risk factor regarding illness severity and clinical outcome during critical illness [5,12]. However, no national or international recommendations exist for vitamin D supplementation in PICU patients.

Enteral nutrition protocols (NP) are recommended to improve the initiation of enteral nutrition, nutritional intake and reduce adverse events in high-risk populations [13]. In our unit, we have been using an evidence-based NP since 2018, supported by the latest guidelines and recommendations, which is updated every two years. The primary goal of this study is to assess whether our NP has improved vitamin D supplementation practices (specifically, the time from PICU admission to initiation and the amount of supplementation). A secondary objective is to compare our vitamin D supplementation approach with national recommendations before and after the implementation of the NP.

2. Materials and Methods

This retrospective monocentric cohort study was conducted at the Lausanne University Hospital, Switzerland. The 12-bed PICU is a mixed medical, cardiac, and surgical unit with approximately 450 admissions annually.

We performed a retrospective data collection on vitamin D doses administered to children aged from 0 to 16 who were admitted to our PICU for more than 48 hours the year before and the year after the introduction of a NP in the unit (implemented in July 2018). Our local ethics committee approved this study (CER-VD project ID 2021-00872). All patients hospitalized for less than 48 hours were excluded from the study.

Physicians prescribe nutritional support, vitamins, and trace elements according to the NP recommendations, which were developed by the medical team and nutritionists of the unit. It recommends nutritional supplementation such as vitamins and trace elements (preferably enteral, as soon as possible, or parenteral when the enteral route is unavailable) for every child admitted to our PICU. As no standard of care for vitamin D supplementation has been established during or after pediatric critical illness, supplementation recommendations were extrapolated from national recommendations for the general pediatric population (FOPH). We use multivitamin complexes to simplify the administration and utilize the galenic forms available, providing the closest doses as recommended (e.g. drops for children under 12, pills for children over 12 years old). The recommended dose of vitamin D supplementation in the NP is: IV 110 IU per day for children <35

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kg, 220 IU per day for children >35 kg; if enteral 444 IU per day for children <12 years old, 200 IU per day for children > 12 years old.

Eligible patients were identified through the PICU mixed register, which meets regulatory and ethical standards applicable to research involving human beings and has been approved by the local ethics committee (CER-VD AO_2021-00001) and the Operational Center for Biobanks and Registries (COB CHUV_2020_009_RM) which is the entity which supports investigators in the implementation of their projects involving the reuse of data and samples in compliance with the legal and ethical framework in our hospital. Data were collected from patients admitted to the PICU before and after implementing the NP and were exported from the Clinical Information System (Metavision, Imdsoft) and the Clinical Information System (Soarian) into an Excel file (coded data). We collected clinical and sociodemographic characteristics of the study population (gender, age, weight at admission, size at admission, length of stay, mortality Pediatric Index of Mortality (PIM) score); timing of introduction of enteral feeding, vitamin D contained in enteral feeding; timing, amount and duration of vitamin D substitution (IU per day), intravenously (IV) and non-IV.

Statistical analysis was performed using Stata 16 program. All values are expressed as numbers (n) and percentages (%), as means and standard deviations for normally distributed data and as medians and interquartile ranges (IQRs) for non-normally distributed data. The Mann-Whitney U test was used for continuous values, and the Pearson's chi-squared test was used for categorical data. According to our analysis and previous nutritional studies in our unit and the literature, we expected a minimum increase of 10% in vitamin D supplementation (IU per patient per day) after the NP implementation. To detect this effect, we estimated that 100 children would be needed in each group to provide the study with a power of 80% and a type one error of 0.05.

3. Results

We collected data from 628 patients, 296 admitted the year before and 332 the year after the implementation of the NP. There was no statistically significant difference in age, gender, weight, size, or length of stay between the two groups. However, there was a difference in the mortality PIM score, with a higher score in the group before the NP implementation (Table 1).

Table 1. Demographics of the two study groups.

	Before nutrition protocol (NP) (n = 296)	After NP (n = 332)	p-value
Gender male/female (%)	170/126 (57.43)	174/158 (52.41)	0.2072
Age (years)	2.29 [0.72 - 7.28]	2.64 [0.48 - 7.12]	0.8380
Weight at admission (kg)	12 [7 - 21.75]	12 [6.15 - 20.2]	0.5020
Size at admission (m)	0.91 [0.68 - 1.18]	0.9 [0.64 - 1.17]	0.5341
Length of stay (days)	5.08 [3.53 - 8.93]	5.13 [3.13 - 8.12]	0.8310
Pediatric Index of Mortality (PIM score)	2.14 [1.02 - 4.41]*	1.40 [0.79 - 3.83]**	**0.0054**

* n = 286 (10 patients did not have a mortality PIM score); ** n = 324 (8 patients did not have a mortality PIM score). All values are expressed as numbers (n) and percent (%), and median and interquartile range (P25-P75). Mann Whitney U test was used to compare the medians between the two populations. Chi square test was used to compare the categorical data.

Total vitamin D administration—including both intravenous (IV) and non-IV supplementation, with or without vitamin D contained in enteral feeding preparations—significantly increased following the implementation of the NP. The mean total daily dose of vitamin D increased from 399 IU/day before NP to 481 IU/day after NP ($p = 0.0007$). Supplemental vitamin D increased from 289 IU/day before NP to 384 IU/day after NP ($p < 0.0001$). However, vitamin D supplementation (IV and non-IV) was not initiated earlier after NP implementation. The median time to initiation remained at

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40 hours from admission in both groups ($p = 0.9$). Notably, a significantly higher proportion of patients received vitamin D supplementation during their stay after NP implementation—95% compared to 77% before ($p < 0.0001$). In the subgroup analysis of patients who did not receive vitamin D supplementation, there was no statistically significant difference in age (6.94 years before NP vs. 7.62 years after NP; $p = 0.4463$) or length of stay (3.75 days before NP vs. 2.96 days after NP; $p = 0.1454$).

The dose of vitamin D supplementation adhered to the local NP recommendations when administered IV, regardless of patient age, and when given orally to patients under 12 years of age. Patients older than 12 years received twice the NP-recommended dose, in alignment with national guidelines (Tables 2 and 3). According to FOPH recommendations for the general pediatric population, vitamin D supplementation (excluding nutritional intake) was adequate in children under one year of age, both before and after NP implementation. However, supplementation was below the recommended doses in children aged 1–3 years. Although patients older than 3 years received less vitamin D than recommended, their supplementation levels increased following NP implementation (Table 3).

Table 2. Vitamin D supplementation compared with nutrition protocol (NP) recommendations.

	Intravenous (IV) vitamin D NP recommendation (IU/day)	**IV administered vitamin D (IU/day of parenteral nutrition)**	**p-value**
Weight at admission <= 35kg (n=26) *	110	110	1.0000
Weight admission > 35kg (n=1) *	220	220	1.0000
	Non-IV vitamin D NP recommendation (IU/day)	**Non-IV administered vitamin D (IU/day of stay being fed)**	**p-value**
Age <= 12 years old (n = 283)**	444	484.36 [231.67 – 576.28]	0.2923
Age > 12 years old (n = 47)**	200	407.27 [459.47 – 580.31]	0.0000

*Patients after protocol implementation who received IV vitamin D supplementation. **Patients after protocol implementation who received non-IV vitamin D supplementation, nutrition excluded. All values are expressed as numbers (n) and median and interquartile range (P25-P75). Mann Whitney U test was used to compare the medians between the two populations.

Table 3. Vitamin D supplementation compared with Swiss Federal Office of Public Health (FOPH) recommendations before and after NP implementation.

	FOPH recommendation (IU/day)	**Vitamin D supplementation (IV and non-IV) before NP (IU/day of stay)**	**p-value**
Age <= 1 year old (n = 91)	400	414.75 [280.11 - 496.44]	0.5852
1 - 3 years old (n = 74)	600	400.92 [210.26 - 568]	0.0000
Age > 3 years old (n = 131)	600	99.31 [0 - 313.02]	0.0000
	FOPH recommendation (IU/day)	**Vitamin D supplementation (IV and non-IV) after NP (IU/day of stay)**	**p-value**
Age <= 1 year old (n = 121)	400	388.25 [201.13 – 522.75]	0.0928
1 - 3 years old (n = 51)	600	419.68 [273.10 – 520.16]	0.0000
Age > 3 years old (n = 160)	600	355.55 [149.33 – 497.86]	0.0000

All values are expressed as numbers (n) and median and interquartile range (P25-P75). Mann Whitney U test was used to compare the medians between the two populations.

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4. Discussion

To our knowledge, this is the first study to demonstrate improved vitamin D supplementation in critically ill children following the implementation of a NP. Given the high prevalence of VDD and its potentially modifiable impact on clinical outcomes in PICU patients, it is noteworthy that a simple intervention can enhance vitamin D administration, allowing to follow national recommendations for the general population better.

Our findings show that, after the NP was implemented, nearly all children admitted to our unit received vitamin D supplementation, compared to 77% prior to its introduction. Since there were no significant differences in age or length of stay between the two groups, it is reasonable to infer that vitamin supplementation became more systematic following the NP, likely due to increased physician awareness of its importance.

Vitamin D supplementation in our unit was administered according to the local NP for all patients receiving it intravenously, and for those under 12 years old when given orally. However, after the NP implementation, patients older than 12 years received an oral dose twice as high as that recommended by the NP. One possible explanation is that most patients were given the multivitamin galenic formulation in drops, intended for children under 12 (which contains double the vitamin D), instead of the pill formulation designed for patients over 12. This higher dose more closely aligns with the national FOPH recommendations for the general population.

A secondary goal of the study was to compare our vitamin D supplementation practices with national recommendations before and after the implementation of the NP. A review of the existing literature revealed no specific national or international guidelines addressing vitamin D supplementation in PICU patients. The Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) in 2017, and the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) in 2020, respectively provided specific guidelines and clinical recommendations for nutrition in critically ill children. The first one does not provide recommendations for vitamin D substitution [14]. The second one declares insufficient evidence to recommend pharmaconutrition in PICU [13]. In 2023, the European Society for Clinical Nutrition and Metabolism (ESPEN) published a practical guideline for clinical nutrition in the intensive care unit. They mention that micronutrients should be provided daily with parenteral nutrition to enable substrate metabolism, and that 25(OH)D status can be determined in all patients considered at risk of vitamin D depletion or deficiency. However, they stated there is uncertainty regarding the dosing and timing of vitamin D administration [15]. Additionally, vitamin D recommendations for the general pediatric population vary considerably between countries. Consequently, we used the national FOPH recommendations for the general population as a reference point for comparison.

When comparing vitamin D supplementation in our PICU to the FOPH recommendations, only patients under one year of age received adequate supplementation both before and after the introduction of the NP. To explain these findings, we hypothesize that, prescribing physicians—most of whom are pediatricians—are more familiar with the SSP recommendations for the general population than with those of the FOPH. Consequently, they recognize the importance of administering vitamin D to infants under one year old but may be less aware of the guidelines for older children. They are probably also aware of the importance of vitamin D for bone metabolism in the early years of life but less aware of the other properties of vitamin D at later ages.

In children older than one year, vitamin D supplementation remained below the FOPH recommendations, despite higher doses being administered after the implementation of the NP compared to before. This finding is unsurprising, given that the vitamin D dosage proposed in the NP for children over one year is lower than the national recommendation. When developing the NP, we took into account the available galenic formulations and prioritized the use of multivitamin complexes to simplify administration. Our results have led to a revision of the NP dosages to improve supplementation rates in accordance with national FOPH guidelines for children over one year of age. Currently, a new multivitamin galenic formulation in milliliters is used in our unit, allowing the administration of 400 IU of vitamin D per day for children under one year old, and 600 IU per day

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for children over one. This highlights the practical challenges of meeting recommended vitamin D requirements using certain galenic forms. To further improve supplementation in children over one, it would be beneficial for clinicians if the SSP and the FOPH harmonized and regularly updated their vitamin D recommendations. Additionally, the PICU medical team needs to recognize that critically ill children are at risk not only of macronutrient deficiencies but also of micronutrient deficiencies. Therefore, they should be considered at risk for hypovitaminosis D and receive appropriate vitamin D supplementation.

These observations highlight the importance of monitoring the correct implementation of a newly introduced protocol and of being able to update it based on monitoring results, emerging evidence and updated recommendations. They also emphasize the need to regularly update and standardize national protocols, as well as promote specialized nutritional knowledge and practices tailored to PICU patients.

This study has several limitations. First, its retrospective and single-center design introduces potential methodological biases. While the pre-post analysis offers valuable insights into the average changes observed during the year following the implementation of the NP, it does not allow us to assess the stability of these changes over time. Second, it would have been helpful to examine additional characteristics of the population that did not receive vitamin D supplementation before and after the NP implementation. For example, evaluating factors such as overall health status (e.g., malabsorption syndromes, renal or hepatic insufficiency, or hypoparathyroidism) could help clarify why some children were not supplemented. The higher PIM score observed in the pre-implementation group, for instance, may suggest that these patients were more severely ill, and that nutritional support was consequently deprioritized.

However, the strengths of our study include the large number of patients enrolled and the short interval between the two study groups, which minimizes the likelihood that other interventions in our PICU may have influenced the results.

It is important to note that we did not assess vitamin D status upon patient admission. As a result, the exact prevalence of VDD in our population remains unknown, and supplementation was not adjusted accordingly. This represents a potential area for improvement and may be worth exploring in future research.

In conclusion, we emphasize the importance of incorporating vitamin supplementation into the overall nutritional strategy of critically ill patients, ensuring that at least the recommended doses for the general population are administered. PICU patients should be regarded as a high-risk group, and efforts should be made to prevent further deterioration of their nutritional and vitamin status during hospitalization. As demonstrated in our unit, the implementation of a NP with specific recommendations can contribute significantly to achieving this objective.

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Ethics approval: This work was approved by the "Commission cantonale (VD) d'éthique de la recherche sur l'être humain" (CER-VD) on the 11th May 2021 (approval code: 2021-00872).

Informed Consent Statement: Informed consent was waived by our Ethics Commission. The research project is a reuse of personal data related to health in the absence of consent, as stated by the Swiss Federal Law (Art. 34 LRH, Art. 37-40 ORH)

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Conflicts of Interest: The authors declare no conflicts of interest.

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Supplementary Materials
Table 1: Demographics of the two study groups.
Table 2: Vitamin D supplementation compared with nutrition protocol recommendations.
Table 3: Vitamin D supplementation compared with FOPH recommendations before and after nutrition protocol implementation.
Nutrition protocol: Protocole d'alimentation et suivi du transit 2018.
Nutrition protocol: Protocole d'alimentation et suivi du transit 2021.

Abbreviations

The following abbreviations are used in this manuscript:

VDD	Vitamin D deficiency
NP	Nutrition protocol
PICU	Pediatric Intensive Care Unit
FOPH	Federal Office of Public Health
SSP	Swiss Society of Pediatrics
IV	Intravenously
PIM	Pediatric Index of Mortality

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