EDITORIAL

Vitamin D Deficiency in Critically Ill Children with Sepsis: What is the Road ahead?

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Vitamin D acts as a steroid hormone with myriad functions in addition to the role in bone mineral metabolism. Vitamin D receptors are present in several tissues including immune system, cardiovascular system, and endocrine system.[1] Hence, the possible role of vitamin D deficiency (VDD) in illness outside of bone mineral metabolism has been the subject of active research for the last two decades.

From the time the first observational study on VDD in critically ill adults was published in 2009 by Lee et al, research in adult critical care has progressed in a frantic pace with several studies including meta-analysis confirming that VDD in critically ill adults is associated with worse outcomes including mortality, length of hospital stay, and need for vasopressors.[2,3] This was followed by intervention studies to check whether vitamin D supplementation in critically ill adults with VDD early in the course results in better outcomes. VITdAL-ICU trial by Amrein et al. published in 2014 failed to show any benefit in outcomes in early supplementation with vitamin D enterally in critically ill adults with 25 OH D levels ≤20 ng/mL compared to placebo.[4] However, subgroup analysis showed a decrease in mortality in the group with severe VDD ≤12 ng/mL. Though the study was underpowered for subgroup analysis, it raised the hope that a subset of patients with severe VDD might benefit from early vitamin D supplementation. However, a much larger, multicenter randomized controlled trial (RCT) (VIOLET) by PETAL study group published in 2019 failed to show any difference in mortality or other clinically relevant outcomes between those who received vitamin D supplementation and those who did not, including the subgroup with severe VDD.[5] The latest meta-analysis on the topic published in 2020 concluded that more studies are needed to confirm the futility of vitamin D supplementation as there was significant heterogeneity in the clinical characteristics of patients in the studies analyzed.[6] Given the fact that VDD is related to inflammation and immune dysfunction, critically ill patients with sepsis and VDD might be the subgroup which could benefit from early supplementation with vitamin D. Meta-analysis published in 2020 on VDD and risk of mortality in adults with sepsis recommended that large clinical trials with adequate sample size for patients with severe VDD (level <12 ng/mL) are needed to evaluate the potential benefits of vitamin D supplementation in patients with critical illnesses and sepsis.[7]

The progress of research in VDD and outcomes in critically ill children is rather slow compared to the adult critical care. Though the first observational study on high prevalence of VDD in critically ill children was published in 2012, subsequent studies, especially the ones from developing countries, have shown inconsistent results on the association between VDD and outcomes like mortality and length of hospital stay.[8–10] This could be due to small sample size, different tests used in analysis of vitamin D levels, different cutoff used for VDD, and the effect of critical illness on vitamin D level like hemodilution and hypoalbuminemia. The gold standard tests for estimating the level of 25(OH)D namely high-performance liquid chromatography and liquid chromatography–tandem mass spectrometry are not available in most centers. The first systematic review of pediatric studies done in 2016 concluded that VDD in critically ill children was associated with worse outcomes including mortality after the data from the studies were pooled.[11]

In this issue of our journal, Ravikiran et al. report the findings of their case–control study on hypovitaminosis D [25(OH)D <30 ng/mL] and parathormone (PTH) response in critically ill children with sepsis. This is an important area of research as sepsis is one of the most common reasons for pediatric intensive care unit (PICU) admission in developing countries and there is paucity of studies in this area. The authors report prevalence of hypovitaminosis D [25(OH)D <30 ng/mL] to be 79.7%, with vitamin D insufficiency [25(OH)D = 21–29.9 ng/mL] to be 59.5%, and VDD [25(OH)D ≤20 ng/mL] to be 20.2%, which is less compared to studies from the north India. This could be because of geographical differences in altitude and latitude, dietary differences, vitamin D level estimation methods used, and differences in underlying diseases.

The authors of the current study did not find any statistically significant association between hypovitaminosis D and worse PICU outcomes namely mortality and PICU stay. This is similar to the study by Ponnarmeni et al. from a tertiary center in North India published in 2016.[9] Recent studies from a tertiary center in South India by Kumar et al. in 2020 showed a significantly higher prevalence of sepsis in critically ill children with VDD. However, mortality was not associated with VDD in multilogistic regression analysis.[12] There could be several reasons for the lack of association of VDD with worse outcomes in the current study. First, the sample size of the study was too small for subgroup analysis on outcomes as discussed by the authors. Second, the cutoff value of vitamin D level selected for analysis was 25(OH)D <30 ng/mL in the study rather than <20 ng/mL used by most studies in the past. The

authors justify the higher cutoff based on the inflection point in PTH curve from linear to plateau at 30 ng/mL level. However, PTH response (>65 pg/mL) was found in only 13.8% of children with levels <30 ng/ mL in this study. Earlier study by Shah et al. in 2016 showed a PTH response (PTH >65 pg/mL) rate of 19.5% using a cutoff of 25(OH)D <20 ng/mL.[10] Both the studies did not find any association between PTH nonresponse and adverse outcomes in those with VDD. The number of children for this subgroup analysis was again too small for any meaningful conclusion.

Recent RCT published in 2020 showed that the administration of 150,000 IU of vitamin D in children with sepsis and VDD (≤20 ng/mL) resulted in lower IL-6, TNF α level, cv-SOFA score, and lower incidence of septic shock compared to those who received placebo.[13] This has opened the possibility of intervention studies in critically ill children with sepsis who have VDD. Lessons learnt from past studies including adult studies in this area can be useful while planning future studies in children. First, large dose of vitamin D should be administered enterally early for its effects to kick in for a meaningful outcome. Second, supplementation is likely to be beneficial in children with severe VDD <12 ng/mL. The sample size should be adequate to give sufficient power to analyze outcomes in this subgroup of children as well as for adjustments for confounding factors. Third, given the low mortality rate in critically ill children, length of hospital stay would be a better primary outcome measure. Fourth, measurements of 25(OH)D and 1, 25 (OH)2D levels 48 hours after administration of vitamin D will help to understand predictors of favorable outcome. Researchers will have to balance the robustness of the methodology with feasibility in planning such a study. Till then, the question whether VDD in critical illness is an innocent bystander or an attributable risk factor for adverse outcome which is amenable for intervention will continue to remain in critical care.[14]

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