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EDITORIAL

Vitamin D deficiency in pediatric critical illness: Time to move on from observational studies?

Deficiencia de vitamina D en pacientes pediátricos críticos: ¿llegó el tiempo de dejar atrás los estudios observacionales?

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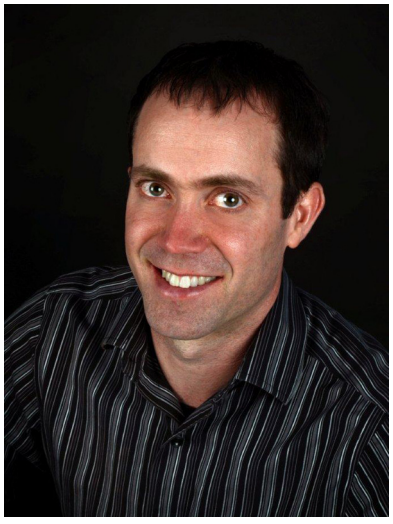

Critical illness occurs in millions of children worldwide each year. Novel means of decreasing mortality, speeding rehabilitation, and reducing long term morbidity would be of great value to the children, their families, and the health care system. Unfortunately, many proposed interventions have limited potential for widespread impact as they target uncommon problems or can be utilized in only a minority of Intensive Care Units (ICUs) due to cost or complexity. In this issue of Revista Chilena de Pediatria, Bustos and colleagues provide data on a new area of research with significant potential to positively impact Pediatric Intensive Care Unit (PICU) outcomes on a global scale.[1] Their study evaluated vitamin D status among critically ill children in Chile, identifying vitamin D deficiency to not only be common but associated with greater illness severity and worse outcome. As eluded to in their discussion, optimization of vitamin D status could represent an ideal means of improving pediatric critical care outcomes both locally and worldwide as supplementation is generally considered safe, simple and inexpensive.

It has been close to 100 years since vitamin D was first identified and deficient body stores convincingly linked to significant bone disease. Moreover, it has been 4 decades since vitamin D was linked to pathology beyond calcium and bone. Since, an impressive number of observational studies and clinical trials have been performed evaluating the role of vitamin D in the health of non-classical organ systems and natural history of related disease processes.

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Given established pleiotropy involving organs central to the development and recovery from critical illness it is somewhat surprising that the ICU community only recently ''discovered'' vitamin D. Consider, for example, that the first ICU observational study suggesting a role for vitamin D was only published in 2009.[2] Since this initial hypothesis generating work the adult research community has wasted little time performing and publishing dozens of observational studies from ICU's around the world. With measurements on tens of thousands of adult subjects, there is now overwhelming evidence that vitamin D deficiency is not only common but associated with worse clinical outcomes, including mortality. Although concerning, these findings have been received as an opportunity and the adult critical care community has proceeded to clinical trials.

But what about the PICU? Optimization of vitamin D status could be just as, if not more, important for the developing child struck by critical illness. Although adult research is relevant, it is important that the pediatric critical care community separately evaluate the importance of vitamin D deficiency and how best to approach supplementation. Ideally, pediatric critical care research on vitamin D would proceed in parallel with adult studies. Regrettably this has not been the case. In contrast to the adult research, the first PICU studies were not published until 2012,[3,4] with vitamin D measurements available from relatively fewer countries and on thousands instead of tens of thousands of patients. Consequently, observational studies like the one performed by Bustos and colleagues continue to make important contributions to the field. For example, their results serve to not only verify findings from previous observational reports, but as the first study from South America, help confirm vitamin D deficiency as a problem on all inhabited continents. In addition, Bustos and colleagues have also contributed important information to the debate about whether vitamin D status is relevant to clinical outcome. In addition to reporting that vitamin D deficiency is associated with greater organ dysfunction, Bustos and colleagues have the distinction of being the first pediatric study to report a statistically significant increase in mortality. Although the mortality findings are consistent with adult research, it is important to emphasize that not all PICU studies have identified relationships between vitamin D and clinical course.[5] The conflicting results may be a consequence of small study sizes and poor power, and a systematic review and meta-analysis has been initiated with goal of pooling data to more precisely define the relationship. Nonetheless, given the well-known issue with confounding in observational studies, clinical trials will be required to definitively determine whether there are benefits to optimizing vitamin D status during critical illness.

The potential value of vitamin D supplementation and need for clinical trials have been recognized by the adult ICU community, as evidenced by the expeditious completion of 8 pilot RCTs and a moderate sized phase III.[6] Again, what about the PICU? To date, outside of a small study focused on severe burns, there are no published clinical trials evaluating high dose vitamin D supplementation in the PICU setting.[7] The reason most likely relates to both the delay in publication of PICU observational studies and uncertainty about how best to supplement vitamin D in the critically ill child. Although amplified in pediatrics, this uncertainty is evident in the adult research community as well. A review of ICU trials performed to date demonstrated significant heterogeneity in the selection of metabolites, dose, and route of administration.[6] Fortunately, the way forward is becoming clear and the PICU research community benefits from these trials. Of the supplementation approaches studied the enteral loading therapy appears the most promising as it not only rapidly and safely normalizes vitamin D status but appeared to improve clinical outcome. In the only phase III RCT to date (VITdAL-ICU), Amrein and colleagues reported that a 540,000 IU enteral cholecalciferol load appeared to decrease mortality and improve long-term functional outcome in vitamin D deficiency critically ill adults.[8] Further in their pilot RCT, Han and colleagues reported that enteral cholecalciferol loading reduced PICU length of stay significantly when compared to the placebo group.[9] Over the past two years, significant progress has been made toward the identification of an appropriate dosing regimen for pediatrics studies. A systematic review and meta-regression of pediatric high dose vitamin D trials demonstrated weight based enteral loading of cholecalciferol at 10,000 IU/kg (maximum 400,000 IU) to be the most appropriate regimen for rapid and safe normalization of vitamin D status.[10] A pilot dose evaluation clinical trial was initiated in 2016 (VITdAL-PICU, clinicaltrials.gov) and recruitment should be complete by the end of 2017.

So what steps remain and when will answers be available for critically ill patients and their health care providers? Not surprisingly, definitive results should come sooner in the adult setting. The same research group that performed the VITdAL-ICU trial has developed a protocol for a large multicenter international phase III adult trial that will focus on confirming that vitamin D supplementation reduces mortality in critically ill patients with severe vitamin D deficiency. In contrast, it is unclear when a large phase III trial will be performed and completed in the PICU setting. In addition to determining the correct loading regimen, the field needs to decide on the outcome measure for the trial. The PICU research community could be tempted to focus on survival, given the positive findings in some observational studies including the one by Bustos and colleagues.[1] Although it is often considered the most important outcome following critical illness, it may not be the best outcome for PICU clinical trials for multiple reasons. First, PICU mortality is often significantly below adult rates, and a focus on survival will lead to large sample size, raising study costs and reducing feasibility. Further, focusing on survival means that any benefits related to other patient oriented outcomes (e.g. health related quality of life) would not be accounted for. This concern is more than theoretical as the adult VITdAL-ICU study suggested that vitamin D deficient patients receiving rapid normalization had improvements in a number of long-term outcomes including risk of respiratory tract infections, falls, and measures of physical functioning.[8]

Increasingly, vitamin D deficiency is being recognized as a problem in the PICU. Critically ill patients, their families and health care providers want an answer to the question about whether to test for and rapidly normalize vitamin D status. Thanks to a dedicated ICU community, like Bustos and colleagues, the answer will come. The question is whether it will come as fast as it could? As a safe, simple and cheap intervention with potential to benefit both critically ill adults and children in ICU's around

the world, this question should become a priority. Time will tell whether it is treated as such.

Conflicts of interest

The author has no conflicts of interest to declare.

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