Clinical Nutrition xxx (2017) 1–9

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Vitamin D supplementation in the critically ill: A systematic review and meta-analysis

Pascal L. Langlois [a], Celeste Szwec [b], Frédérick D'Aragon [a], Daren K. Heyland [c, d], William Manzanares [e, *]

[a] Department of Anesthesiology and Reanimation, Faculty of Médecine and Health Sciences, Sherbrooke University Hospital, Sherbrooke, Québec, Canada
[b] Department of Nutrition, Hospital A. Posadas, Buenos Aires, Argentina
[c] Clinical Evaluation Research Unit, Kingston General Hospital, Kingston, ON, Canada
[d] Department of Medicine, Queen's University, Kingston, ON, Canada
[e] Department of Critical Care, Intensive Care Unit, University Hospital, Faculty of Medicine, UDELAR, Montevideo, Uruguay

ARTICLE INFO

Article history:
Received 18 December 2016
Accepted 6 May 2017

Keywords:
Vitamin D
Critically ill
Cholecalciferol
Calcitriol
Meta-analysis

SUMMARY

Introduction: Vitamin D insufficiency is reported in up to 50% of the critically ill patients and is associated with increased mortality, length of stay (LOS) in intensive care unit (ICU) and hospital, and respiratory disorders with prolonged ventilation. Benefits of vitamin D supplementation remain unclear. The aim of this systematic review was to evaluate the clinical benefits of vitamin D administration in critically ill patients.

Methods: We searched Medline, Embase, CINAHL and Cochrane database for randomized controlled trials (RCT) conducted on heterogeneous ICU patients comparing vitamin D administration to placebo. Evaluated outcomes included mortality, infectious complications, hospital/ICU LOS and length of mechanical ventilation. Two independent reviewers assessed eligibility, risk of bias and abstracted data. Data was pooled using a random effect model to estimate the relative risk (RR) or weighted mean difference. Pre-defined subgroup analysis included oral-enteral vs. parenteral administration, high vs. low dose, vitamin d deficient patient, high vs. low quality trials.

Results: Six RCTs (695 patients) met study inclusion. No reduction in mortality was found (P = 0.14). No differences in ICU and hospital LOS, infection rate and ventilation days existed. In the subgroup analysis, the oral-enteral group, there was no improvement in mortality (P = 0.12) or hospital LOS (P = 0.16). Daily doses >300,000 IU did not improve mortality (P = 0.12) and ICU LOS (P = 0.12).

Conclusions: In critically ill patients, Vitamin D administration does not improve clinical outcomes. The statistical imprecision could be explained by the sparse number of trials.

1. Introduction

Vitamin D is a fat-soluble vitamin that is synthesized in the skin in response to sunlight exposure and then converted in the liver to 25-hydroxyvitamin D3 or cholecalciferol, which is mainly transformed by the kidneys in 1, 25-dihydroxyvitamin D also known as calcitriol. Vitamin D participates in bone mineral metabolism through the modulation of calcium and phosphorous levels. Moreover, in recent years an increased body of research has shown the biological effect of vitamin D on cardiac function through reduced remodeling and fibrosis secondary to a negative regulation of renin by vitamin D receptor (VDR)-linked gene regulation and through reduced cardiac metalloproteinase activities [1]. VDR are also expressed on immune cells (T and B cells, monocytes/macrophages, mast cells and antigen-presenting cells). In murine models, VDR-deficient mice supplemented in calcium exhibited a grossly deficient immune system susceptible to infections and autoimmune diseases, a high renin hypertension, cardiac hypertrophy, increased thrombogenicity [1]. In human, similar findings exist but clear functional explanation and solid association is still missing. According to current literature, normal level of vitamin D is defined by serum cholecalciferol greater than 30 ng/mL [2,3], whereas

* Corresponding author. Universidad de la República (UdelaR), Hospital de Clínicas (University Hospital), Department of Critical Care, Intensive Care Unit, Italia Ave, 14th Floor, Montevideo, 11.600, Uruguay. Fax: +598 24877213.
E-mail address: wmanzanares@adinet.com.uy (W. Manzanares).

http://dx.doi.org/10.1016/j.clnu.2017.05.006
0261-5614/

Please cite this article in press as: Langlois PL, et al., Vitamin D supplementation in the critically ill: A systematic review and meta-analysis, Clinical Nutrition (2017), http://dx.doi.org/10.1016/j.clnu.2017.05.006

serum level lower than 30 ng/L define vitamin D insufficiency, whilst deficiency is generally described when it is under 20 ng/L [4].

So far, several observational studies have demonstrated that 50% of critically ill adult patients exhibit vitamin D deficiency, with undetectable levels in almost 17% [3]. These epidemiologic numbers are only slightly higher than general population in America, but are well higher than European statistics [5,6]. In the critical care setting, this deficiency has been associated with adverse outcomes such as infections, longer length of stay, acute kidney injury and higher mortality [7,8]. In 2014, in a systematic review and meta-analysis, Haan et al. [9] identified vitamin D deficiency as a risk factor for severe infections and mortality in the critically ill, whereas another meta-analysis [10] found an association between vitamin D deficiency and mortality in intensive care unit (ICU) patients. Nonetheless, in a recently published study of patients with severe sepsis and septic shock, vitamin D deficiency was not associated with 90-day mortality [11]. So far, the role of vitamin D in the critically ill has not yet been fully understood [12]. Moreover, it remains unknown whether vitamin D deficiency in ICU patients is an epiphenomenon, a marker of illness severity, or is a major contributor of mortality and morbidity with direct causative effects. A good mean of evaluating the presence of vitamin D in the causal pathway is to evaluate if administration improves the mortality/morbidity.

Over the past six years, few randomized controlled trials (RCT) have evaluated the effect of high-dose vitamin D3 therapy using different dose regimens provided by oral, enteral, and parenteral route in critically ill patients [7,12–16]. While the original rationale was to administrate Vitamin D in order to restore the normal body content, many trials also supplemented at supra-physiological level, supporting the concept of pharmaconutrition [12–16]. So far, clinical results of these interventional studies have been inconclusive. With regard to current recommendations, in 2015 the Canadian Clinical Practice Guidelines (CPGs) concluded that there were insufficient data to make a recommendation about vitamin D therapy in the critically ill patient [17], whereas the most recent American Society for Parenteral and Enteral Nutrition (ASPEN)/Society of Critical Care Medicine (SCCM) guidelines, based on expert consensus suggest that fat soluble vitamins substitution, including vitamin D, should be considered in ICU patients with history of bariatric surgery accordingly to the recommended dietary allowance (RDA) due to their high risk of vitamin deficiencies but do not support administration in other patients [18]. No precision regarding high-dose supplementation of vitamin D was mentioned.

Putzu et al. [19] have recently published a systematic review and meta-analysis on vitamin D supplementation in the serious illness. However, the authors included one trial that reported biochemical outcomes and another trial of non-critically ill patients. Moreover, in another meta-analysis of vitamin D therapy Weng et al. [20] after aggregating 4 trials found a significant reduction in hospital length of stay (LOS). Nonetheless, this meta-analysis did not include all the studies evaluating the overall efficacy of vitamin D supplementation on clinical important outcomes in critical care. Thus, we conducted an updated and comprehensive systematic review and meta-analysis of all RCT evaluating high dose vitamin D therapy on relevant clinical outcomes in adult critically ill patients.

2. Methods

2.1. Search strategy and study identification

A literature search was conducted in Embase, CINAHL, Medline, the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews to identify all randomized controlled trials (RCTs) published between 2000 and September 2016. No language restrictions were applied and broad search terms were used to find references corresponding to the following words and MeSH headings: “randomized,” “clinical trial,” “critical care”, “critically ill”, “supplementation”, “therapy”, “cholecalciferol”, “calcitriol” and “vitamin D”. The reference lists of the relevant articles were also reviewed to ensure adequate study identification.

2.2. Eligibility criteria

Trials were eligible if they corresponded to the following characteristics:

1. Study design: randomized controlled trials (RCTs) with parallel groups. The trial had to report the primary outcome, hospital mortality, or any of the secondary outcomes, including ICU and hospital LOS, mechanical ventilation days and infection rates as defined by the authors. If hospital mortality was not reported, 30-day mortality was used to complete the meta-analysis.
2. Population: adult patients (≥18 years of age) hospitalized in the ICU, including medical, surgical and neurologic ICU. If ambiguous, a population was considered critically ill if the reported mortality rate was higher than 5% in the control group.
3. Intervention: oral, enteral or parenteral vitamin D administration as 1, 25-dihydroxyvitamin D (calcitriol) or 25-hydroxyvitamin D (cholecalciferol).
4. Comparator: either placebo or a vitamin D administration included in standard nutritional therapy.
5. Outcomes: the trial was required to report any clinical outcomes in ICU patients between mortality, infectious complications, length of ventilation including invasive and non-invasive MV, ICU and hospital length of stay (LOS). Trials reporting only biochemical outcomes were excluded.

2.3. Eligibility review and data abstraction

Two reviewers (PLL and CS) independently screened citation and evaluate the full text of potentially eligible studies in duplicate, then abstracted data onto customized, pre-tested forms. Disagreements between reviewers were resolved through discussion or third party adjudication.

2.4. Assessment of risk of bias

For every included RCT, the methodological quality was assessed in duplicate by two independent reviewers using a data abstraction form with a scoring system from 0 to 14 (see Supplementary material) according to the following criteria:

1. Concealed randomization
2. Extent of blinding
3. Intention-to-treat analysis (ITT)
4. Baseline group comparability
5. Loss to follow-up
6. Description of the studied intervention
7. Similarity of co-interventions between groups
8. Pre-specified and pre-defined clinical outcomes

Reviewers reached consensus for every methodological score obtained during data abstraction. When the trials were only available as abstract, when the published paper was in a language impossible for us to read or when data was missing for adequate data abstraction, trials' authors were contacted to obtain additional details. We designated a trial as a level 1 study if all of the following criteria are fulfilled: concealed randomization, blinded outcome

Please cite this article in press as: Langlois PL, et al., Vitamin D supplementation in the critically ill: A systematic review and meta-analysis, Clinical Nutrition (2017), http://dx.doi.org/10.1016/j.clnu.2017.05.006