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Original Research

High dose vitamin D administration in ventilated intensive care unit patients: A pilot double blind randomized controlled trial

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ABSTRACT

Background: There is a high prevalence of vitamin D deficiency in the critically ill patient population. Several intensive care unit studies have demonstrated an association between vitamin D deficiency [25-hydroxyvitamin D (25(OH)D) < 20 ng/mL] and increased hospital length of stay (LOS), readmission rate, sepsis and mortality.

Material and Methods: Pilot, double blind randomized control trial conducted on mechanically ventilated adult ICU patients. Subjects were administered either placebo, 50,000 IU vitamin D_3 or 100,000 IU vitamin D_3 daily for 5 consecutive days enterally (total vitamin D_3 dose = 250,000 IU or 500,000 IU, respectively). The primary outcome was plasma 25(OH)D concentration 7 days after oral administration of study drug. Secondary outcomes were plasma levels of the antimicrobial peptide cathelicidin (LL37), hospital LOS, SOFA score, duration of mechanical ventilation, hospital mortality, mortality at 12 weeks, and hospital acquired infection.

Results: A total of 31 subjects were enrolled with 13 (43%) being vitamin D deficient at entry (25(OH)D levels < 20 ng/mL). The 250,000 IU and 500,000 IU vitamin D_3 regimens each resulted in a significant increase in mean plasma 25(OH)D concentrations from baseline to day 7; values rose to 45.7 ± 19.6 ng/mL and 55.2 ± 14.4 ng/mL, respectively, compared to essentially no change in the placebo group (21 ± 11.2 ng/mL), $p < 0.001$. There was a significant decrease in hospital length of stay over time in the 250,000 IU and the 500,000 IU vitamin D_3 group, compared to the placebo group (25 ± 14 and 18 ± 11 days compared to 36 ± 19 days, respectively; $p = 0.03$). There was no statically significant change in plasma LL-37 concentrations or other clinical outcomes by group over time.

Conclusions: In this pilot study, high-dose vitamin D3 safely increased plasma 25(OH)D concentrations into the sufficient range and was associated with decreased hospital length of stay without altering other clinical outcomes.

Introduction

There is a high prevalence of vitamin D deficiency in the critically ill patient population, with approximately 60% of patients found to be vitamin D deficient, (25(OH)D concentrations <20 ng/mL), and an additional 30% of patients being vitamin D insufficient, (25(OH)D = 20–30 ng/mL) [1–10]. Several intensive care unit (ICU) studies have demonstrated an association between vitamin D deficiency and important clinical outcomes: increased hospital length

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Abbreviations: 1,25-dihydroxyvitamin D, 1,25(OH)2D3 = calcitriol; 25 (OH)D, 25-hydroxyvitamin D; AMP, antimicrobial peptides; APACHE II, acute physiology and chronic health evaluation II; BALF, bronchial alveolar lavage fluid; HAI, hospital acquired infection; IU, international units; LOS, length of stay; MAP, mean arterial pressure; SOFA, sequential organ failure assessment

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of stay (LOS), readmission rates, sepsis and mortality [3–9,11,12]. Vitamin D deficiency is also associated with increased risk of acute respiratory failure in critically ill patients [13,14]. Furthermore, Dancer et al. found that vitamin D deficiency is nearly universal in the development of acute respiratory distress syndrome and mechanistically related to lung inflammation and alveolar epithelial cell injury [15].

Vitamin D has pleiotropic effects on the host immune pathway and may be uniquely involved with lung immune function and alveolar capillary barrier function. In monocytes and macrophages, pathogens bind to cell surface toll-like receptors to CYP27b1 stimulate to convert 25(OH)D, the biomarker of vitamin D status, into the active form 1,25-dihydroxyvitamin D [1,25$(OH)_2D_3$; calcitriol]. 1,25$(OH)_2D_3$ in turn upregulates mRNA expression of human cationic antimicrobial protein (hCAP-18), which is cleaved to produce LL-37, a major anti-microbial peptide (AMP) with activity against gram-positive/gram-negative bacteria, fungi and viruses [16–18]. Although data are inconsistent, existing evidence suggests that supplementation with vitamin D_3 may decrease susceptibility or enhance recovery to infections such as influenza, recurrent pneumonia and tuberculosis [19–21].

An observational study in patients with serum 25(OH)D < 20 ng/ml found that improved vitamin D status before hospital admission decreased the odds of all cause-mortality [22]. A recent large randomized study by Amrein et al. demonstrated decreased mortality in a subgroup of subjects with severe vitamin D deficiency (<12 ng/ml) given a one-time bolus dose of 540,000 IU of enteral cholecalciferol [23]. Leaf et al. found that lower plasma 25(OH)D levels on admission to the ICU correlated with lower LL-37 plasma levels that were, in turn, associated with increased 90 day mortality and sepsis risk [24,25]. In addition, a single intravenous dose of 2 μg calcitriol in adult ICU patients with severe sepsis or shock significantly upregulated leukocyte mRNA for hCAP-18 and the anti-inflammatory cytokine interleukin-10 24 hours after dosing [24,26]. Therefore AMPs may be important modifiers of the immune response in critically ill patients in response to vitamin D status or exogenous administration.

We designed this pilot study to evaluate the safety and efficacy of two doses of vitamin D_3, 250,000 or 500,000 IU, given in divided doses over 5 consecutive days to increase plasma 25(OH)D concentrations to the sufficient range (>30 ng/mL) and to increase plasma LL-37 in adult ventilated patients requiring intensive care.

Methods

Trial design

The study was approved by the Emory University Institutional Review Board and written informed consent was obtained from the patient or legal surrogate prior to study enrollment. The enrollment goal of this pilot study was 36 patients (12 in each group) from two Atlanta, Georgia hospitals; Emory University Hospital (EUH) and Emory University Midtown (EUH-M). The study was registered at www.clinicaltrials.gov (NCT01372995) and the protocol was amended to include bronchoscopy at both baseline and study day 7. A Data Safety Monitoring Board reviewed progress and adverse event reports every 6 months during the duration of the trial. The entire study duration was 84 days; however, blood samples were only taken every 7 days while the patient was hospitalized.

Participant selection

Enrollment started in July 2011 and was completed in March 2014. Inclusion criteria were: 1) receiving care in an ICU; 2) age greater than 18 years; 3) expected to require mechanical ventilation for at least 72 hours after study entry; 4) expected to survive and remain in the ICU for at least 96 hours after study entry; and 5) enteral access in place to enable delivery of vitamin D_3 or placebo and are deemed to be able to tolerate enteral drug administration. Exclusion criteria were: 1) inability to obtain or declined informed consent from the subject and/or legally authorized representative; 2) current pregnancy; 3) ongoing shock, [defined as unstable blood pressure despite vasopressor support and mean arterial pressure (MAP) < 60 mm Hg on at least 3 consecutive readings within a 3-hour period prior to study entry]; 4) current hypercalcemia (albumin-corrected serum calcium > 10.8 mg/dL or ionized calcium > 5.2 mg/dL); 5) history of therapy with high-dose vitamin D_3 (greater than or equal to 50,000 IU a week) to treat vitamin D deficiency, within previous 6 months; 6) history of disorders associated with hypercalcemia (history of cancer with history of hypercalcemia within the past 1 year, hyperparathyroidism, sarcoidosis, nephrolithiasis); 7) chronic dialysis; 8) known history of cirrhosis; 9) known HIV; and 10) received any investigational drug within 60 days prior to study entry. The initial protocol included bronchoscopy on day 7 of intubation, but the protocol was amended to include a baseline bronchoscopy and then a repeat on days 5–7 if the patient remained intubated, in order to increase our sample size. The protocol was amended in January 2012 to permit enrollment of any adult critically ill mechanically ventilated patients.

Intervention

Following informed consent, subjects' Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated [27]. Treatment assignments were stratified according to clinical center and dichotomized APACHE II score ≤ or >15. Subjects were randomly assigned in a 1:1:1 ratio to placebo or a total of 250,000 IU vitamin D_3 or 500,000 IU vitamin D_3 in divided equal doses over 5 days.

Treatment groups were assigned by a blinded block randomization schedule overseen by biostatisticians of the Atlanta Clinical and Translational Science Institute (ACTSI) biostatistics core. The placebo arm received two inactive medication tablets daily for 5 days; treatment arm 1 received one 50,000 international units (IU) of vitamin D_3 and 1 placebo pill daily for 5 days (250,000 IU total) and treatment arm 2 received 2 pills of 50,000 IU of vitamin D_3 daily for 5 days (500,000 IU total). The medications were dissolved in sterile water and administered through an enteral feeding tube. Cholecalciferol 50,000 IU tablets were manufactured from Tischon (Westbury, NY) and Biotech (Fayetteville, AR) and bioavailability testing conducted during the trial showed the capsules to be within 10% of the stated dose. EUH and EUH-M Investigational Drug Service pharmacists maintained the code and delivered all study drugs to the respective study subject's primary nurses for administration per research protocol. With the exception of the pharmacists, all study staff were blinded to the group allocation.

Clinical and demographic characteristics

Clinical and demographic data were collected at baseline. Sequential organ failure assessment (SOFA) [28] scores, laboratory values and other clinical data were collected daily while the subjects were hospitalized. Hospital-acquired infections (HAI) were measured as a composite of all infectious complications that occurred during hospitalization according to the 2009 Center Disease Control definitions [29]. Measured safety parameters included serial serum creatinine, calcium, and phosphorous concentrations, and adverse events.