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Vitamin D and Delirium in Critically Ill Patients: A Preliminary Investigation

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Abstract

Purpose—The pathophysiology of delirium in critical illness is unclear. 25-OH vitamin D (25-OHD) has neuroprotective properties but a relationship between serum 25-OHD and delirium has not been examined. We tested the hypothesis that low serum 25-OHD is associated with delirium during critical illness.

Materials and methods—In a prospective cohort of 120 medical ICU patients, blood was collected within 24 hours of ICU admission for measurement of 25-OHD. Delirium was identified once daily using the Confusion Assessment Method for the ICU. Multivariable logistic regression

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was used to analyze the association between 25-OHD and delirium assessed the same day and the subsequent day after 25-OHD measurement, with adjustments for age and severity of illness.

Results—Median age was 52 years (IQR, 40, 62), and APACHE II was 23 (IQR, 17, 30). Thirty-seven patients (41%) were delirious on the day of 25-OHD measurement. 25-OHD levels were not associated with delirium on the day of 25-OHD measurement [OR 1.01, 95% CI: 0.98–1.02] or on the day after measurement (OR 1.01, 95% CI: 0.99–1.03).

Conclusions—This pilot study suggests that 25-OHD levels measured early during critical illness are not important determinants of delirium risk. Since 25-OHD levels can fluctuate during critical illness, a study of daily serial measurements of 25-OHD levels and their relationship to delirium during the duration of critical illness may yield different results.

Keywords

25-OH vitamin D; delirium; acute brain dysfunction; critical illness; intensive care unit

Introduction

Delirium is an acute brain dysfunction affecting up to 80% of mechanically ventilated ICU patients and is associated with prolonged hospitalization, increased costs, higher short- and long-term mortality [1], and long-term cognitive impairment [2]. An accurate understanding of delirium pathogenesis in the ICU is currently lacking. Research has focused on neuro inflammation, direct drug exposure (e.g., sedatives and analgesics), and alterations in neurotransmission (e.g., amino acid perturbations) as potential mechanisms, but most studies to date have been preliminary in nature [3–5].

The role of vitamin D in critical illness has recently received close attention. Multiple studies of community-dwelling elderly persons [6] have shown associations between vitamin D deficiency and cognitive outcomes, including dementia. Older age appears to be a determinant of lower vitamin D levels in community-dwelling elderly patients [7]. Small observational studies have documented widespread vitamin D deficiency in up to 80% of critically ill patients [8–11], and two large multicenter observational studies found that 25-OHD levels both pre-morbidly and at critical care initiation were significant predictors of short and long-term mortality for ICU patients [12;13]. A preliminary study [11] has shown that vitamin D levels in critical illness drop by about 10–15% within the first 7 days of critical illness. Vitamin D is thought to play an important role in neurogenesis and possesses pleiotropic anti-inflammatory properties [14]. The latter might be critical in explaining the pathogenesis of delirium in critically ill patients who are frequently admitted to an ICU with conditions characterized by severe systemic inflammation such as sepsis or the acute respiratory distress syndrome (ARDS) [3;15]. Additionally, 25-OHD modulates function of microglial cells (macrophages in the brain and an important source of pro-inflammatory cytokines). Microglial activation has been reported [15] as one of the main hypotheses of delirium pathogenesis. Microglia activation is usually involved in a normal host defense against central nervous system infection but over-activation of this system for example during sepsis or ARDS can lead to a self-propelling neuro inflammatory reaction with production of inflammatory cytokines. Vitamin-D has been shown in vitro to down regulate the production of TNF- α , IL-6 and nitric oxide through the presence of vitamin-D receptors on microglia [16].

Taken together, these data led us to hypothesize that low serum 25-OHD at ICU initiation would be associated with delirium, an acute form of cognitive impairment among critically ill patients. In particular we evaluated an association between 25-OHD and delirium in the early phase of critical illness (i.e. on the day of and on the day after 25-OHD measurement).

Methods

Study Design and Population

This prospective cohort study was nested within the Validating Acute Lung Injury biomarkers for Diagnosis (VALID) study, a large, ongoing prospective cohort study designed to evaluate plasma biomarkers for the diagnosis of acute lung injury/acute respiratory distress syndrome (ARDS) in critically ill patients. All patients enrolled in the VALID study at Vanderbilt University Medical Center (Nashville, TN) who were assessed for delirium by one of two investigators (RRM and TDG) were included in this investigation. All ICU patients were eligible for inclusion in VALID except for those 1) <18 years of age, 2) in an ICU >3 days before enrollment, 3) post-cardiac arrest, 4) with a history of severe chronic lung disease, or 5) admitted to the ICU for an uncomplicated overdose or routine postoperative admission after cardiothoracic surgery. In addition, enrolled patients who died or were discharged from the ICU within 48 hours of admission were removed from the study, since VALID is designed to study patients at high risk to develop ARDS.

When possible, informed consent was obtained from the participant (if capable) or an available surrogate. In addition, because the study involved minimal risk to participants, the institutional review board at Vanderbilt University, which approved the study protocol, waived the requirement for informed consent if the participant was not capable and no surrogate was available.

Exposure, Covariates, and Outcomes

Blood for measurement of serum 25-OHD concentration, the primary exposure variable, was collected at the time of study enrollment (i.e., within 24 hours of ICU admission and within 3 hours of the first delirium assessment by study personnel), then centrifuged within 1 hour of collection and stored at -80° Celsius (C). Serum 25-OHD concentrations were measured in duplicate by chemiluminescence immunoassay (Heartland Assays, Ames, Iowa).

Clinical covariates were selected *a priori* based upon prior research and biological plausibility, and given the sample size, limited to two in number: age and severity of illness (Acute Physiology and Chronic Health Evaluation II -APACHE II) score [17].

One of two trained intensivists (RRM or TDG) assessed each patient once daily for delirium, the primary outcome, using the Confusion Assessment Method for the ICU (CAM-ICU) [18]. Level of consciousness was assessed using the Richmond Agitation-Sedation Scale (RASS) [19]. Patients were categorized as comatose if they were unresponsive to verbal and physical stimuli (RASS -5) or responsive only to physical stimuli (RASS -4); they were considered delirious if they were not comatose (i.e., RASS -3 to +4) and had a positive CAM-ICU assessment.

Statistical Analysis

Baseline demographics and clinical characteristics are presented using medians and interquartile ranges for continuous variables and proportions for categorical variables. For descriptive purposes, 25-OHD was classified as severely deficient (<25 nmol/L), deficient (25 to <50 nmol/L), insufficient (50 to <75 nmol/L), or sufficient (≥75 nmol/L) [6], but 25-OHD was analyzed as a continuous variable in the multivariable model. There is not a formal definition of vitamin D deficiency in critically ill patients. We have used widely accepted cut-off in the literature [6] and also as recently reported by the Institute of Medicine [20].

In our primary analysis, we examined the association between 25-OHD concentrations and the probability of delirium on the day of 25-OHD measurement using multiple logistic regression. In a secondary analysis, we examined the association between 25-OHD concentrations and delirium on the day following 25-OHD measurement. For both analyses, we included only patients who could be assessed for delirium; comatose patients were excluded. We restricted both analyses to the first two days of delirium assessments since 25-OHD levels might change during the course of critical illness[21].

To adjust for potential confounders, age and APACHE II score were included in all regression models as covariates. Log-transforming 25-OHD did not improve model fit or change results. We therefore report results from models using non-transformed values of 25-OHD.

We also conducted a sensitivity analysis considering 25-OHD as categorical (see above) [6] where “sufficient” 25-OHD (≥ 75 nmol/L) was the reference group, to further evaluate the association between delirium and specific categories of 25-OHD levels.

All statistical analyses were performed using STATA version 11 (<http://www.stata.com/stata11/>).

Results

A total of 120 patients were enrolled and evaluated for delirium between February 2006 and February 2007. Baseline demographics and clinical characteristics of these patients are noted in Table 1 and reflect a critically ill population with a median APACHE II score of 23 (Interquartile range 17–30). Spearman correlations found no association between the APACHE-II score and 25-OHD levels (*Spearman's rho*=0.18) suggesting that vitamin D levels are not mere markers of severity of illness. On the day of enrollment and 25-OHD measurement, 29 (24%) patients were comatose, precluding delirium assessment at that time. Of the remaining 91 patients who were assessable, 37 (41%) were delirious.

25-OHD concentrations were not associated with delirium on the day of 25-OHD measurement ($p=0.78$) (Table 2). 25-OH vitamin D concentrations were also not associated with delirium (Table 2) on the day after 25-OHD measurement ($p=0.49$).

Categorizing 25-OHD levels resulted in no qualitative differences: insufficient [Odds Ratio (OR) 0.53, 95% Confidence interval (CI): 0.1–2.5], deficient (OR 0.76, 95% CI: 0.18–3.15), and severely deficient (OR 0.68, 95% CI: 0.15–3.14) levels of 25-OHD were not associated with delirium.

Discussion

In this pilot investigation, the first to our knowledge evaluating the relationship between 25-OH vitamin D levels and delirium, serum 25-OH vitamin D levels early during critical illness were not associated with delirium on the day of 25-OHD measurement or the day following. These results suggest that 25-OHD levels are not important determinants of delirium risk early during critical illness.

Deficiency of 25-OHD has been estimated to be prevalent in over 80% of critically ill patients[8]. The role of 25-OHD might indeed be promising in delirium due to 25-OHD's pleiotropic and immunomodulatory properties, extra renal activation and ubiquitous distribution of the vitamin D receptor (including in neurons, astrocytes, and oligodendrocytes [22–24])[8]. Indeed one of the leading hypotheses of delirium pathogenesis is linked to a neuroinflammatory derangement, leading to a neuroinflammatory cascade with

activation of pro-inflammatory cytokines and chemokines with an exaggerated inflammatory response and eventually to neuronal death. 25-OHD is considered an important potential co-factor in the prevention of neurodegeneration as it plays a key role in neurogenesis and expression of neurotrophic factors and also in B-amyloid clearance - key elements in the pathophysiology of Alzheimer's Disease [25]. 25-OHD is also considered to be neuroprotective through immunomodulation and antioxidative mechanisms [8]. Studies from animal models have shown that 25-OHD reduces pro-inflammatory cytokines (e.g., TNF- α) and increases anti-inflammatory cytokines (e.g., interleukin-10) in human and animal models [26–28]. The possible reduction of neuroinflammation linked to 25-OHD suggests a promising biologic (and possibly a novel therapeutic) role for 25-OHD in delirium during critical illness, a hypothesis that has not yet been investigated.

In our pilot investigation, however, we did not find an association between 25-OHD and delirium among critically ill patients. Our results echo those of Slinin and colleagues [29], who found that vitamin D levels were not associated with cognitive outcomes in a study of community living elderly patients. It is possible that the neuroprotective effects of vitamin D are important for some domains of cognition, such as executive function, [30] but not for those that are typically deranged during delirium. Though there have been several prospective and retrospective observational studies evaluating the association between vitamin D and cognitive impairment in older adults, [31] we still need placebo-controlled trials to establish if vitamin D supplementation will protect against cognitive decline not only in older adults but also, if a relationship will be established, potentially in long-term cognitive impairment following a critical illness. Alternatively, the cognitive effects of vitamin D may be dwarfed during critical illness, when patients experience numerous insults that can affect the brain; i.e., in the setting of profound systemic inflammation, metabolic derangements, exposure to deliriogenic medications, and environmental changes, levels of vitamin D may have relatively little short-term effect on brain function.

This study has strengths along with limitations. The strengths of the study include 1) a robust methodology for delirium assessment using a validated tool, the CAM-ICU [18], which was performed by two trained intensivists; 2) clear and consistent time-points for 25-OHD sampling thereby allowing evaluation of a strict temporal relationship between sampling and delirium; 3) the ability to adjust for important confounders of delirium such as APACHE-II score, itself an independent risk factor for delirium in our cohort ($p=0.01$); and 4) a diverse study population representative of the critical care population at large (including medical and surgical critical care patients) with high median APACHE II scores and a high prevalence of delirium.

Limitations of this study include a patient cohort drawn from a single medical center, which may reduce the generalizability of our findings. Also, a relatively small sample size limited the number of covariates we could include in the regression models, since inclusion of additional covariates—such as factors that may alter vitamin D levels (e.g., albumin concentration, volume of fluid resuscitation) [21] or risk factors for delirium (e.g., pre-existing functional and cognitive impairment, sedation regimen) [32]—might result in an overfit regression model, i.e., produce false positive results. Because vitamin D concentrations were measured at only one time point, we could not assess whether acute changes in vitamin D concentrations during critical illness have a different relationship with delirium than vitamin D levels at a single time point. Higgins [11] reported a diminution of vitamin D levels in critically ill patients progressively over a period of days. Different hypothesis have been postulated including low sunlight exposure, and insufficient nutrition during critical illness (enteral or otherwise), but we still lack a definitive understanding. In cardiac surgery patients, Krishnan and colleagues [21] found a drop in vitamin D levels after haemodilution and loss of colloid oncotic pressure; the vitamin D levels, however, returned

almost to baseline levels after the surgery. The investigators hypothesized that massive haemodilution secondary to cardiac by-pass or changes in vitamin D binding protein (VDBP), may results in lower 25-OHD levels[33]. Therefore future studies evaluating the effect of 25-OHD changes during critical illness should include a daily measurement of 25-OHD and VDBP levels over the course of an ICU stay to provide further insight on the specific role of this vitamin on risk of delirium over time.

The results of our study might not be generalizable to an older or non-ICU population, but they provide an opportunity to investigate this association in other settings. It is important, finally, to acknowledge the possibility of type II error (i.e., a false negative); we found no signal whatsoever between 25-OHD levels and delirium, but our study was limited in size and scope. A larger study should be performed to confirm this lack of association, though such a study might more fruitfully focus on changes in 25-OHD and VDBP levels during critical illness and delirium risk. Additionally, larger studies could clarify if there could be an association in a subgroup population among whom 25-OHD is a risk factor (e.g. older patients),

Conclusions

Our investigation did not show an association between serum levels of 25-OHD measured early in the course of critical illness and the development of delirium. This pilot investigation provides a useful starting point for dissecting the possible role of vitamin D in cognitive outcomes in critically ill patients. Because 25-OHD levels can fluctuate during critical illness, future studies with daily serial 25-OHD and VDBP measurements over time might better define the association between vitamin D and delirium, if indeed such an association exists at all. Additionally, even if low vitamin D levels during critical illness are not associated with delirium, they could put ICU survivors at increased risk for poor long-term cognitive outcomes, a potential association which has yet to be examined.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Characteristics of 120 critically ill ICU patients.*

Variables	Cohort (N=120)
Age	52 (40,62)
Male, n (%)	72 (60%)
Caucasian, (%)	98 (82%)
APACHEII	23 (17,30)
ICU length of stay, days	5 (3,10)
Hospital length of stay, days	9 (6,19)
Mechanical ventilation, n (%)	69 (58%)
Admission diagnoses	
-Sepsis	52 (43.3%)
-Gastrointestinal bleed	17 (14.1%)
-Altered mental state	12 (10%)
-Trauma	8 (6.7%)
-Other gastrointestinal ^a	8 (6.7%)
-Other cardiovascular ^b	6 (5%)
-Other pulmonary ^c	6 (5%)
-Other metabolic ^d	4 (3.3%)
-Other ^e	7 (5.9%)
Delirium prevalence on day 1, n (%)	37 (41%) ^f
25-OH vitamin D (nmol/L)	38 (26, 56)
25-OH vitamin D classification, n (%) ^g	
- Sufficient (≥ 75 nmol/L)	13(10.8%)
-Insufficient (≥ 50 & < 75 nmol/L)	29 (24.2%)
-Deficient (≥ 25 & < 50 nmol/L)	50 (41.7%)
-Severely deficient (< 25 nmol/L)	28 (23.3%)

* Median and interquartile range (IQR) unless otherwise noted.

Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II ; Acute respiratory distress syndrome, ARDS; Myocardial infarction, MI; Congestive heart failure, CHF; chronic obstructive pulmonary disease, COPD

^aOther gastrointestinal: pancreatitis, hepatic failure, perforated oesophagus^bOther cardiovascular: hypertensive crisis, congestive heart failure^cOther pulmonary: asthma, chronic obstructive pulmonary disease, pulmonary embolism, airway obstruction^dOther metabolic: diabetic ketoacidosis, hypoglycemia^fOf 91 patients who were not comatose and could therefore be assessed for delirium.^gTo convert nmol/L to ng/ml divide by 2.5.

Table 2
Association between plasma vitamin D levels and delirium in critically ill ICU patients.

Variable	Model 1			Model 2		
	25-OH Vitamin D and delirium on day the sample was drawn	OR ^a	95% CI	25-OH Vitamin D and delirium on day the sample was drawn	OR ^a	95% CI
25-OH Vitamin D, nM/L		1.01	0.98–1.02		1.01	0.99–1.03
Age		0.99	0.96–1.01		0.99	0.95–1.02
Apache-II		1.09	1.03–1.17		1.10	1.03–1.18

^aThe odds ratio (OR) reflects the relative change in odds of delirium associated with a one-unit increase in each independent variable included in the multivariable logistic regression model. For example, a 1-point increase in APACHE-II was associated with a 9% increase in the odds of delirium on the day of enrollment, after adjusting for 25-OH vitamin D levels and age. Alternatively, 25-OH vitamin D levels were not associated with delirium, whether assessed on the day of enrollment or the following day.

Abbreviation: APACHE II, Acute Physiology and Chronic Health Evaluation II.