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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 intensive care unit (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 was used to analyze the association between 25-OHD and delirium assessed the same day and the subsequent day after25-OHD measurement, with adjustments for age and severity of illness.

☆ Conflicts of interest: None.

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Results: Median age was 52 years (interquartile range, 40-62), and Acute Physiology and Chronic Health Evaluation II was 23 (interquartile range, 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 (odds ratio, 1.01; 95% confidence interval, 0.98-1.02) or on the day after measurement (odds ratio, 1.01; 95% confidence interval, 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.

1. 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 neuroinflammation, direct drug exposure (eg, sedatives and analgesics), and alterations in neurotransmission (eg, 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-OH vitamin D (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]. In addition, 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 neuroinflammatory reaction with production of inflammatory cytokines. Vitamin-D has been shown in vitro to down regulate the production of tumor necrosis factor α, interleukin 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 (ie, on the day of and on the day after 25-OHD measurement).

2. Methods

2.1. 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/ARDS in critically ill patients. All patients enrolled in the VALID study at Vanderbilt University Medical Center (Nashville, TN, USA) who were assessed for delirium by one of 2 investigators (RRM and TDG) were included in this investigation. All ICU patients were eligible for inclusion in VALID except for those (1) younger than 18 years, (2) in an ICU more than 3 days before enrollment, (3) who have had 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 because 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.