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Effects of vitamin D deficiency in critically ill surgical patients

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Abstract

BACKGROUND: The incidence of vitamin D deficiency in critically ill patients is reported to be up to 50%, with a 3-fold increase in predicted mortality, but limited data exist concerning vitamin D deficiency in critically ill surgical patients.

METHODS: Sixty-six adult surgical intensive care unit patients who had 25-hydroxyvitamin D serum levels evaluated from January 2010 to February 2011 were prospectively identified. Patients were divided into groups according to vitamin D level ($<$20 vs $\geq$20 ng/mL).

RESULTS: Of the 66 patients evaluated, 49 (74%) had vitamin D levels $<$ 20 ng/mL, and 17 (26%) had vitamin D levels $\geq$ 20 ng/mL. Patients with vitamin D levels $<$ 20 versus $\geq$ 20 ng/mL had longer lengths of hospital stay. Lengths of intensive care unit stay were clinically longer, although not significant. Infection rates tended to be higher ($P = .09$), and a higher incidence of sepsis was seen in the patients with vitamin D levels $<$ 20 ng/mL.

CONCLUSIONS: Vitamin D levels $<$ 20 ng/mL have a significant impact on length of stay, organ dysfunction, and infection rates. More data are needed on the value of supplementation to improve these outcomes.

Vitamin D deficiency has increased in the general population over the past decade.[1] Critically ill patients are at an increased risk for progressive vitamin D deficiency because of lack of exposure to sunlight and dietary supplementation.[2] Vitamin D insufficiency in intensive care unit (ICU) patients may be as high as 50%, with undetectable levels seen in 17%.[3] Recently, a large trial reported that deficiency in vitamin D was a significant predictor of short-term and long-term all-cause patient mortality and blood culture positivity in a critically ill patient population.[4] Vitamin D plays an important role in many different physiologic functions. The primary and most well known function of vitamin D is to maintain calcium and phosphorus homeostasis and promote bone mineralization. However, there is an increasing amount of literature focusing on the pleiotropic effects of the vitamin, such as immune modulation, endothelial and mucosal functions, and glucose metabolism.[1,5] Vitamin D

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deficiency has been associated with myocardial infarction, diabetes, autoimmune disease, chronic obstructive pulmonary disease, neoplasm, tuberculosis, and increased mortality in the general population.[2] This deficiency has translated to severe hypocalcemia and increased risk for mortality in critically ill patients. Furthermore, it may lead to other morbidities, such as hyperglycemia, organ dysfunction, and increased susceptibility to nosocomial infections.[2] It is necessary to examine whether vitamin D deficiency or insufficiency is a risk factor for increased morbidity and mortality in surgical critically ill patients.

The purpose of this study was to evaluate the effects of vitamin D deficiency on the associated risk for mortality, end-organ dysfunction, infections, and length of stay in the critically ill surgical patients.

Methods

Study population

This institutional review board–approved, prospective, observational study included adults aged ≥ 18 years admitted to the surgical ICU for ≥48 hours. The study period was from January 1, 2010, through February 28, 2011. Serum vitamin D (25-hydroxyvitamin D) levels were drawn on admission and every 7 days for the duration of hospitalization. Vitamin D supplementation was provided if the patient was able to receive oral administration of medications. The electronic medical records of these patients were reviewed to collect all other pertinent laboratory data. Patients were stratified according to vitamin D level. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D level < 20 ng/mL and sufficiency as ≥20 ng/mL, with the normal range being 30 to 100 ng/mL.[6]

Statistical analysis

Data were evaluated using descriptive statistics in SPSS version 17.0 (SPSS, Inc, Chicago, IL). Categorical data were analyzed using Pearson's χ^2 or Fisher's exact tests, and continuous data were analyzed using Student's *t* tests or Mann-Whitney *U* tests as appropriate. *P* values < .05 were considered statistically significant.

Results

A total of 66 consecutive adult patients admitted to the surgical ICU who met our inclusion criteria and had 25-hydroxyvitamin D serum levels were evaluated. The major reason for exclusion was not being in the ICU for >48 hours. The patients were 56 ± 20 years of age, 65% were men, and 71% were African American. In addition, the overall Acute Physiology and Chronic Health Evaluation (APACHE) II score was 17 ± 7, and 48% of patients were admitted with trauma-associated injuries. Of the 66 patients evaluated, 49 (74%) had vitamin D levels < 20 ng/mL, and 17 (26%) had vitamin D levels ≥ 20 ng/mL, with only 3 patients having a levels > 30 ng/mL. Fifty percent of patients received oral vitamin D supplementation. Baseline characteristics were not different between the groups (Table 1).

Table 1 Baseline characteristics

Characteristic	Vitamin D level (ng/mL) <20 (n = 49)	≥20 (n = 17)	*P*
Age (y)	59 ± 15	68 ± 18	.06
APACHE II score	16.6 ± 7.3	17.1 ± 5.3	.67
Hypertension	18 (36%)	3 (17%)	.22
Hypercoagulable state	12 (25%)	7 (23%)	.22
Diabetes mellitus	11 (23%)	1 (6%)	.16
Coronary artery disease	6 (13%)	2 (12%)	1.00
Cancer, any type	5 (11%)	3 (17%)	.41
Parathyroid hormone (pg/mL)	102 ± 94	205 ± 181	.03
Calcium, ionized (mmol/L)	1.16 ± 0.09	1.14 ± .1	.21
Magnesium (mg/dL)	1.7 ± .4	1.7 ± .2	.85
Phosphorus (mg/dL)	3.6 ± 1.4	3.1 ± .8	.18
Glucose (mg/dL)	151 ± 81	128 ± 37	.36
Blood urea nitrogen (mg/dL)	21 ± 17	27 ± 15	.10
Creatinine (mg/dL)	1.6 ± 1.8	1.7 ± 1.5	.43
Albumin (mg/dL)	2.4 ± .5	2.4 ± 0.6	.77

Data are expressed as mean ± SD or as number (percentage).

Overall, the in-hospital mortality rate was 7% (5 of 66), with no differences between groups. Patients with vitamin D levels < 20 versus ≥ 20 ng/mL had longer lengths of hospital stay (29 ± 27 vs 17 ± 14 days, $P = .03$). Lengths of ICU stay were also longer but did not reach statistical significance (19 ± 26 vs 13 ± 13 days, $P = .30$).

Infection rates were higher with in patients with vitamin D levels < 20 ng/mL compared with those with levels ≥ 20 ng/mL (43% [26 of 49] vs 29% [5 of 17], $P = .09$). In addition, a higher incidence of sepsis was found, although this was not significant (37% [18 of 49] vs 23% [4 of 17], $P = .29$). When evaluating the various types of infection, pneumonia was most common (13 of 66 [20%]), followed by intra-abdominal infections (5 of 66 [8%]). No difference was seen between the groups when analyzing bacteremia, pneumonia, urinary tract infection, skin–soft tissue infection, or intra-abdominal infection.

In patients who had >1 vitamin D level (24 of 66 [36%]), only 11 (45%) had improvements in their vitamin D levels of ≥50% over the course of their hospitalization. In patients who had oral vitamin D supplementation and had >1 vitamin D level, only 8 of 24 patients (30%) had increases in their vitamin D levels of ≥50%, but only 3 of 24 (12%) had vitamin D levels > 30 ng/mL.

Table 2 Variables affected by vitamin D deficiency

Characteristic	Vitamin D level (ng/mL) <20 (n = 49)	≥20 (n = 17)	P
Length of hospital stay (d)	29 ± 27	17 ± 14	.03
Length of ICU stay (d)	19 ± 26	13 ± 13	.30
Overall infections	26 (53%)	5 (29%)	.09
Sepsis	18 (36%)	4 (23%)	.29
Age ≥ 60 y	13 (26%)	10 (59%)	.01
Body mass index ≥ 30 kg/m^2	14 (28%)	2 (12%)	.16
In-hospital mortality	3 (6%)	2 (12%)	.59

Data are expressed as mean ± SD or as number (percentage).

Of the 49 patients with APACHE II scores ≥ 18, 21 patients had vitamin D levels < 20 ng/mL, and 28 had levels ≥ 20 ng/mL. In the 21 patients with vitamin D levels < 20 ng/mL plus APACHE II scores ≥ 18 compared with patients with vitamin D levels ≥ 20 ng/mL plus APACHE II scores ≥ 18, length of hospital stay (49 ± 36 vs 13 ± 13 days, $P < .0001$) and length of ICU stay (34 ± 32 days vs 7 ± 11 days, $P < .0001$) were longer. Additionally, infection rates were higher in this subset of patients (76% [16 of 21] vs 35% [10 of 28], $P = .005$).

Age ≥ 60 years was the only significant factor associated with VDL ≥ 20 ng/ml ($P = .01$). Body mass index ≥ 30 kg/m^2 trended toward significance in this group ($P = .16$; Table 2). No significant differences were seen between baseline magnesium, phosphorus, ionized calcium, or creatinine level. Interestingly, parathyroid hormone levels were higher in patients with vitamin D levels ≥ 20 ng/mL on admission (205 ± 181 vs 102 ± 94 pg/mL, $P = .03$; Table 1). Most patients were discharged home.

Comments

Vitamin D deficiency causes myriad systemic effects in surgical ICU patients. Our patients had associated increased lengths of hospital and ICU stay, as well as higher infection rates. This correlates with other studies.[4]

In contrast, the mortality rate was not higher with vitamin D deficiency, as has been recently described.[4] Perhaps this is due to the smaller number of comorbid conditions in our population. Additionally, parathyroid hormone levels were higher at admission in those with higher vitamin D levels. Normally, parathyroid hormone level will increase as serum vitamin D level decreases. Is this difference due to the physiology of vitamin D deficiency in critical illness? We also found no episodes of calcium derangements, ruling out multisystem organ failure, tertiary hyperparathyroidism, or any other form of hyperparathyroidism.[7]

Because of the ubiquitous nature of vitamin D, with its many areas of function, the question remains: is vitamin D deficiency is a syndrome to be repleted, a marker of severe illness, or both? There are vitamin D receptors on Toll-like receptors overseeing immune function.[8] Vitamin D is fat soluble; thus, it enters into cells acting as a possible steroid hormone to govern hormonal pathways, immune function, and cellular proliferation.[9] This explains its pleiotropic effects. Thus, vitamin D deficiency in patients who are severely ill, defined as an APACHE II score ≥ 18, most likely cause an additive effect on patient outcomes of infection and lengths of stay.

Only 12% of our patients who received vitamin D supplementation achieved serum vitamin D levels > 30 ng/mL. A recent review discussed the safety and efficacy of vitamin D supplementation. The investigators suggested that vitamin D supplementation may need to exceed >1,000 U/d to provide an adequate response in serum vitamin D levels.[10] Hence, we do not know if the repletion of vitamin D provides an improvement in outcomes. This question has not yet been answered in randomized trials.[11] Because of its many roles, vitamin D insufficiency and/or deficiency should be evaluated and treated.

There were limitations to our study, which included a relatively small sample size in this surgical intensive care population. Because 70% of our patients were African American, our patient population could be predisposed to vitamin D deficiency in the normal state of health. Hence, this factor may have confounded our results.

Conclusions

Vitamin D deficiency in critically ill surgical patients is an important problem. Vitamin D levels < 20 ng/mL have a significant impact on length of stay, organ dysfunction, and infection rates. More data are needed on the value of supplementation to improve these outcomes.

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Discussion

Dr Mary C. McCarthy (Dayton, OH): In your selection of 20 as cutoff, did you look at some of the other populations as a control rather than just looking at low levels in your population in the ICU? Do you have a control population, and how do those levels in your patient population compare with a control? Could low levels just be a surrogate marker for disease states, gender, race and BMI? Could these findings be related to the osteopenia seen in ICU patients? Finally, since vitamin D is important in the intestinal calcium absorption only when the dietary intake is low, and we usually correct calcium in the ICU, do you think that vitamin D is actually all that important or is that actually the calcium and phosphorous levels that are the important factor?

Dr Heather Dolman (Detroit, MI): We did not have a control group that we looked at and just prospectively evaluated patients that came in over this time period. Our population is biased because they do have these factors that make them more prone to vitamin D deficiency, obesity and African American race, making a control group difficult. The second question, is vitamin D just a marker for obesity? That's the big question, is it a marker for all these disease states for obesity, coronary artery disease, diabetes? The body has vitamin D receptors all over and many tissues also have the enzyme to convert vitamin D to its active form, so you wonder if it plays more than just the role of a vitamin. It has pleiotropic effects, gene related effects to effect immunomodulation and the like, but in addition, it also acts as a hormone, so perhaps we just haven't figured out how exactly it works in people who are ill. As to the low vitamin D related to osteopenia in ICU patients, these levels were levels drawn at admission. Numbers were too small to evaluate vitamin D levels on a weekly basis in those still in the ICU. How vitamin D works is interesting and it actually might act more than as just a vitamin and as a hormone with multiple effects all over. Electrolyte values were normal, so we were trying to rule out any other factors, like hypocalcemia or hyperphosphatemia or the like, or even hyperparathyroidism as being a cause of what we're seeing. I think that we're just seeing vitamin D deficiency, and it probably should be replaced.

Dr Arthur M. Carlin (Detroit, MI): You also need to keep in mind about seasonal variations in sunlight, so important for vitamin D levels.

Dr Dolman: We didn't look at seasonal variations.