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Vitamin D in Critical Illness – Fifty Shades of VIOLET

Did the VITDALIZE study and the VIOLET study manage to answer some of the questions regarding vitamin D deficiency and its impact on critically ill patients? Experts compare the findings and present an overview.

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Introduction

Vitamin D deficiency is very common in the ICU (usually >60%) because many critically ill patients were already chronically ill before their acute illness. Current guidelines recommend low doses < 1000 IU daily for supplementation and standard diet for critically ill patients contains less vitamin D than recommended for healthy individuals. Vitamin D is not a vitamin at all but a steroid hormone - it possesses its own nuclear vitamin D receptor which is expressed in many cell types; with sufficient UV-B exposure the body can produce enough endogenous vitamin D from cholesterol in the skin.

> **“ is it really conceivable that an inconspicuous substance such as vitamin D can have a mortality benefit in the event of serious illness? ”**

A large number of epidemiological studies link vitamin D deficiency to many diseases across a wide variety of organ systems. Following the publication of a letter in the New England Journal of Medicine in 2009, the vitamin D hype also reached the intensive care unit (ICU) (Lee et al. 2009).

Starting in 2011, several randomised controlled intervention studies were published; the Austrian VITDAL-ICU study (n=480) (Amrein et al. 2014) was the largest study on this topic until the recent publication of VIOLET. Results of the VITDAL-ICU study showed no difference in the primary endpoint regarding the length of hospital stay (LOS). A surprisingly large mortality benefit in the predefined subgroup with severe vitamin D deficiency was found (25-hydroxyvitamin D (25OHD) <12ng/ml, n=200).

The logical next step was to plan the VITDALIZE study, which started in Austria in 2017 and was extended to Belgium in 2019 (protocol: Amrein et al. 2019). In parallel, the VIOLET study was started in the USA in 2017, which was prematurely terminated in 2018 and recently published. The results were rather sobering. Were all important questions answered? Is the hype over?

The VIOLET Study: A Short Summary

The VIOLET study was a randomised controlled, double-blind, placebo-controlled phase III trial within the US PETAL network. Patients with vitamin D deficiency and high risk of developing ARDS and mortality were administered enteral vitamin D3, recruiting mainly in the emergency department (ED), likely because 1) early administration was considered to be better and 2) the PETAL network focuses on ED patients.

The protocol adopted the same enteral loading dose of cholecalciferol as VITDAL-ICU and the same definition of vitamin D deficiency (25OHD < 50nmol/l). In total, 3000 adults with vitamin D levels of 25(OH)D≤20ng/ml were to be recruited in the emergency room when ICU admission was "scheduled" and patients meet criteria for being at risk for ARDS and mortality. Vitamin D levels were measured at inclusion using a POCT device but only individuals with mass spectrometrically verified D deficiency (25(OH)D<20ng/ml) were included in the final analysis. Subjects were randomised in a 1:1 ratio and treated with high-dose enteral vitamin D3 (once 540,000 IU) or a placebo. The primary endpoint 90-day mortality was 23.5% in the vitamin D group (125 of 531) and 20.6% in the placebo group (109 of 528), (95% confidence interval, -2.1 to 7.9; p=0.26). There were no clinically relevant differences between the groups in terms of secondary clinical, physiological or safety endpoints (National Heart, Lung, and Blood Institute PETAL Clinical Trials Network et al. 2019). On the positive side, a loading dose of 540,000 IU of vitamin D has not led to any negative consequences for patients.

While the VIOLET study originally specified a sample size of 3000, the publication only reports on the findings from 1360 patients who were recruited and randomised. The target number of 3000 was not reached because the study was prematurely terminated after the first interim analysis (which was obviously conducted later than planned) due to "futility." Ultimately, only 1078 patients met all inclusion criteria.

In a subgroup of patients with 25(OH) D levels <12 ng/ml, the placebo group seemed to perform better. This is in complete contrast to VITDAL-ICU's results and appears contradictory to the large body of evidence suggesting stronger effects of vitamin D in more severe deficiency. The subgroup analysis did not show clear signals. Ironically, however, especially in the group with ARDS before study entry, mortality seemed to be lower in the placebo group. However, it should be noted that due to the unadjusted multiple testing with 21 subgroup analyses in two populations, the probability of type 1 error is very high.

Discussion

Although with only a cursory inspection the VIOLET and VITDALIZE studies appear to be very similar, there are important differences **(Table 1)** that continue to spark hope for benefit from vitamin D administration in the ongoing European VITDALIZE study. The studies also answer different questions. The protocol of the VITDALIZE trial was recently published in BMJ Open in 2019 (ClinicalTrials.gov Identifier: NCT03188796).

There are a number of substantial differences between VIOLET and VITDAL/VITDALIZE which could explain the outcome difference:

Single ultra-high loading dose without maintenance doses

An appropriately high loading dose is absolutely necessary in acute situations in order to quickly increase vitamin D levels. However, it is extremely unphysiological to administer a high loading dose without a maintenance dose. Recent findings demonstrated shorter effects of some metabolites. Vitamin D catabolism is also stimulated and it is conceivable that there is less at the end than at the beginning. Several studies also showed a higher risk of falls and fractures; Martineau et al. (2017) demonstrated a lack of effect on respiratory infections (compared to daily or weekly doses). For these reasons, paradigms shifted away from – admittedly handy – high-dose treatments with long intervals.

Study population

In the VITDAL-ICU study, a mortality benefit was only found in the subgroup with severe vitamin D deficiency with an initial value of 25-hydroxyvitamin D level <12ng/ml (200 of 480 patients). These findings were not taken into account in VIOLET.

Work highly relevant on this matter was published by London pulmonologist Adrian Martineau (2017) in the BMJ. In an individual patient data meta-analysis of almost 11,000 people, he was able to show that vitamin D can prevent respiratory tract infections, but only if administered daily or weekly.

	VIOLET	VITDALIZE
SITES	USA, > 40 sites	Europe (Austria, Belgium, Germany, UK)
Population	Patients planned for ICU	ICU patients
Vitamin D at inclusion	25(OH)D<20ng/ml	25(OH)D<12ng/ml
Intervention	Cholecalciferol 540,000 IU enterally	Cholecalciferol 540.000IU enterally. Maintenance: 4000IU enterally once daily up to day 90
Placebo	Placebo (MCT)	Placebo (MCT)
Primary Endpoint	**90-day mortality**	**28-day mortality**
Sample size	planned n=3000 actual n=1078 (stopped at first interim analysis)	planned n=2400 current: >450 (recruiting)

Table 1. Factbox: VIOLET vs. VITDALIZE

The strongest effect with a number needed to treat (NNT) of only 4 (!) was observed in people with severe vitamin D deficiency at baseline.

The "Goldilocks" Effect

For an endpoint such as mortality, it must be assumed that an intervention can only be effective for people with a moderate disease severity - individuals who are "too healthy" may recover with or without intervention. Conversely, individuals "too ill" may die with or without intervention. This is similar to potential benefits of wearing a helmet in case of rockfall, where the size of the falling rock may determine the usefulness of said helmet.

Although an ultra-early intervention seems to make sense in principle, it probably makes it very difficult to assess the trajectories of the individual, i.e. whose outcome could potentially be altered (just as, for example, the duration of ventilation and the usefulness of a tracheotomy is very difficult to predict).

Is it really conceivable that an inconspicuous substance such as vitamin D can have a mortality benefit in the event of serious illness? There is already a Cochrane meta-analysis that showed a mortality benefit of several percent (6% for all-cause and 12% for cancer mortality) in healthier individuals (mostly older women in osteoporosis studies) (Bjelakovic et al. 2014). For critically ill patients with a higher event rate and a high risk of "second hits" such as nosocomial infections, a mortality benefit seems possible.

> **"the topic of vitamin D deficiency and vitamin D in diseases requiring intensive care is and will therefore remain a hot topic"**

The topic of vitamin D deficiency and vitamin D in diseases requiring intensive care is and will therefore remain a "hot topic." Even a mortality benefit of 1% would be relevant (however, much larger studies are still needed for this; VITDALIZE is "only" powered to an absolute difference of 5%). In any case, vitamin D is too harmless and too inexpensive not to be investigated seriously.

In Canada, the VITDALIZE Kids study has recently been launched, which is a multi-centre study to investigate the effect of vitamin D on morbidity endpoints (@ vitdalizekids, ClinicalTrials.gov Identifier: NCT03742505).

VITDALIZE and VITDALIZE kids will hopefully shed more light on this important topic in the next years. ■

Key Points

- Vitamin D deficiency is very common in the ICU because many critically ill patients were already chronically ill before their acute illness.
- A large number of epidemiological studies link vitamin D deficiency to many diseases across a wide variety of organ systems.
- VITDAL-ICU study was the largest study on this topic until the recent publication of VIOLET.
- The VIOLET study was a randomised controlled, double-blind, placebo-controlled phase III trial conducted with patients with vitamin D deficiency and high risk of developing ARDS.

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