Title: Early High-Dose Vitamin D3 for Critically Ill, Vitamin D–Deficient Patients

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Introduction & Aim

A randomised, multicentre, double-blind, placebo-controlled trial evaluating the efficacy of early administration of high-dose vitamin D3 for critically-ill patients with low serum vitamin D levels.

Methods

Randomised patients received either 540,000IU in a single dose of enteral vitamin D or placebo within 12 hours of ICU admission. They were randomised if they had a vitamin D level <20ng/mL.

The primary end-point was 90 day all-cause mortality. Secondary end-points included ventilator-free days to day 28 and quality of life to day 90.

Results

Of 2624 patients recruited, 1360 (52%) screened positive for vitamin D deficiency and were randomised. Approximately one-third were mechanically ventilated in each group, and the most common qualifying conditions were pneumonia, sepsis and shock. 84% of randomised patients were medical ICU patients.

The trial was stopped early due to futility. There was no significant difference in the primary or any of the secondary end-points. Mortality was nonsignificantly higher for the vitamin D group (23.5% *vs* 20.6%, p=0.26) across several subgroups including those with sepsis, pneumonia and acute respiratory distress syndrome.

Discussion

A major strength of the trial is that its design minimises bias. The patient age, comorbidities and acute issues are typical of a medical ICU cohort. Crucially, the primary end-point chosen is unambiguous and important in this cohort of critically ill patients. This trial did not receive industry funding.

A major weakness is the very high dose of vitamin D given for treatment, which is not in keeping with most major clinical guidelines for treatment of vitamin D deficiency (50,000IU weekly for 6-8 weeks, followed by maintenance dosing). Point-of-care vitamin D testing used for trial recruitment is not widely available. While the trial had an ethnic mix representative of the US population, this is not similar to the Irish population which limits applicability.

Given vitamin D's wide availability and low cost, it is tempting to hope it might improve outcomes in those who are critically ill. This study should give us pause for thought. There are other trials underway examining vitamin D in different ICU cohorts and to examine efficacy in covid-19 patients.

This is an important trial to consider given we will be treating increased numbers of critically ill patients due to the current covid-19 pandemic. Pending further data, I will err on avoiding treating vitamin D deficiency in critically ill patients unless they have clinically significant hypocalcemia or symptoms.