Safety of long term bolus dose Vitamin D supplementation: data from a randomized controlled trial (ViDA)

Zarintaj Malihi.[1] Carlene M.M Lawes[1], Debbie Waayer[1], Les Toop[2], Kay-Tee Khaw[3], Carlos A. Camargo Jr. [4], Robert Scragg[1].

1. Department of Epidemiology and Biostatistics, School of Population Health, The University of Auckland.
2. Department of General Practice, The University of Otago, Christchurch, New Zealand.
3. Department of Public Health, University of Cambridge, Cambridge, England.
4. Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.

Abstract. Many clinical trials have investigated the beneficial effects of vitamin D supplementation over the past few decades. However, little is known about safety of long term bolus dose supplementation of this vitamin. This paper investigated the safety of long term high monthly supplementation with vitamin D. Monthly vitamin D supplementation with 100,000 IU for a median period of 3.3 years did not increase self-reported adverse events in middle-aged and older adults.

Introduction

Vitamin D supplementation is being used increasingly in higher doses in randomized controlled trials (RCTs). However, two RCTs have shown increased risk of falls from very large annual doses of vitamin D, while a third trial found that low dose vitamin D, with calcium supplements, increased kidney stone risk (Sanders et al. 2010; Smith et al. 2007; Jackson et al. 2006).

Objective

To identify if there is any increased risk of adverse effects, measured using self-reports, from taking long term high bolus doses of vitamin D3 supplements in an RCT of 5110 adults living in Auckland, New Zealand (ViDA study).

Methods

Participants aged 50-84 years were recruited mainly from family practices in Auckland during 2011-2012. Participants were excluded if they had hypercalcaemia at baseline (serum calcium >2.50 mmol/L), any history of sarcoidosis, kidney stones, gastric bypass surgery, were already on vitamin D supplementation of >600IU/d in 50-70 year olds and >800IU/d in >70 year olds, or had other disease complications or situations that would interfere with their participation in the study for 3 years.

After the baseline assessment, 5110 participants were randomized to receive either 100,000 IU vitamin D3 or placebo capsules. Participants were mailed a capsule every month from the study start till Jun 2013 which changed to four capsules every four month from Jul 2013 till the study end in Jul 2015.

A questionnaire was included in the envelope with the capsules, in which participants answered questions about their health status during the previous month. This had an open-ended question that asked about any side effects that the participant attributed to the capsule during the previous month. Based on the reported events, study specific categories were developed by a study clinician to code events into broad symptom categories.

This research explores the frequency of adverse events reported by participants to determine whether participants in the vitamin D arm reported specific types of adverse events differently from those in the placebo arm. In addition, it compares incidence rates of adverse events between participants in vitamin D and placebo arms.

Data analysis was done using SAS statistical analysis package (version 9.4). Poisson and negative binomial regression methods were used in logistic regression analyses. Hazard ratio of time to the first event was calculated using Cox-regression models in SAS.

The study methods have been published previously. (Scragg et al. 2016; Scragg et al. 2017).

Results

Of the 5110 people randomized, 2558 were in the vitamin D arm and 2552 in the placebo arm. Subsequently, two participants in the placebo arm withdrew their consent. Another 52 people never returned any questionnaire, leaving 5056 participants in this analysis.

Overall, 566 participants reported adverse events: 288 in the vitamin D arm, and 278 in the placebo arm. There was no significant difference between study arms in the number of people reporting one or more adverse events (p=0.61).

A total of 1108 adverse events were reported. There was no difference in the frequency of reported events between the vitamin D and placebo groups (Table 1).

Table 1: Number of adverse events reported by participants in the vitamin D and placebo groups.

Number of adverse events	**Treatment**			
	Vitamin D	Placebo	Total	*P
No event	2120 (83.5)	2118 (84.1)	4238	0.20
1 event	195 (7.7)	203 (8.1)	398	
2 events	65 (2.6)	72 (2.9)	137	
3 events	45 (1.7)	42 (1.7)	87	
4 events	72 (2.8)	54 (2.1)	126	
5 events	9 (0.35)	11 (0.4)	20	
≥ 6 events	33 (1.3)	17 (0.7)	50	
Total	2539	2517	5056	

These events were distributed across eight symptom categories as shown in Figure 1 which includes recurrent events. The most prevalent adverse event was pain, with about 150 events in each arm. This was followed by infection and respiratory/infection, dizziness, gastrointestinal, skin, tiredness, and other events.

Many adverse events were reported as related to other known health conditions, such as hypertension, diabetes, and post-surgery complications.

Participants in the vitamin D arm did not report significantly more side effects than the placebo arm for any of the reported categories of adverse events ($p>0.05$), except for the category of dizziness and issues with balance and vision, which was slightly more common in the vitamin D arm (Figure 1).

Nevertheless, the numbers of participants who reported this event, being 43 and 36 in vitamin D and placebo arm, respectively, were not significantly different between arms (hazard ratio=1.18; 95% CI=0.76, 1.83; p=0.47). Nor was the incidence risk ratio (IRR) significantly increased in the vitamin D compared with the placebo arm (IRR=1.66; 95%CI= 0.94, 2.92; p=0.08).

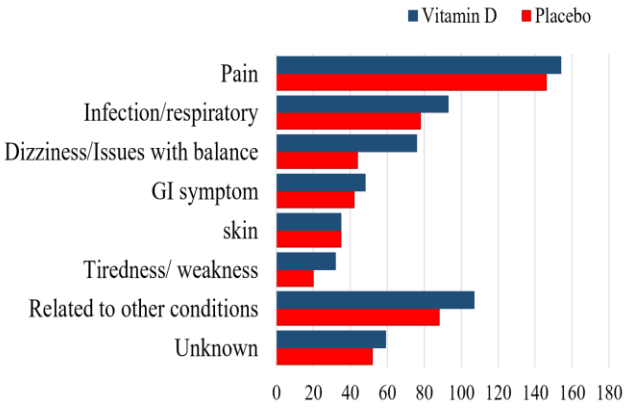

Figure 1. Type and frequency of adverse events from vitamin D supplementation per treatment arm.

In multivariate analyses, age and ethnicity were found to be associated with reporting of adverse events, with Maori and Pacific Islands participants having an increased risk of reporting adverse events compared with European ($p<0.01$). Similarly, there was a weak but significant direct association between age and reporting of adverse events ($p<0.01$).

The number of participants who dropped out of the study was not different between the study arms (p=0.45). Among the reasons provided by participants for withdrawing from the study, having an adverse event was reported by only six participants, all of whom were in the placebo arm.

Participants were also asked about their perception of whether they had been allocated to take vitamin D or placebo. There was no difference in allocation perception between treatment arms (p=0.52). In addition, the proportion of participants who reported an adverse event did not vary with allocation perception.

Conclusions

Monthly vitamin D supplementation with 100,000 IU for a median period of 3.3 years did not increase self-reported adverse events in middle-aged and older adults. There was a non-significantly higher risk of recurrent dizziness events in vitamin D arm. Further large RCTs are required to confirm the results of this study.

References

Jackson, R.D., LaCroix, A.Z., Gass, M., Wallace, R.B., Robbins, J., Lewis, C.E., Bassford, T., et al. 2006. Calcium plus vitamin D supplementation and the risk of fractures. New England Journal of Medicine 354: 669–83.

Sanders, K.M., Stuart, A.L., Williamson, E.J., Simpson, J.A., Kotowicz, M.A., Young, D., Nicholson, G.C. 2010. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 303: 1815–22.

Scragg, R., Waayer, D., Stewart, A.W., Lawes, C.M.M., Toop, L., Murphy, J., Khaw, K-T., Camargo, C.A. Jr. 2016. The Vitamin D Assessment (ViDA) study: design of a randomized controlled trial of vitamin D supplementation for the prevention of cardiovascular disease, acute respiratory infection, falls and non-vertebral fractures. Journal of Steroid Biochemistry and Molecular Biology 164: 318–25.

Scragg, R., Stewart, A.A., Waayer, D., Lawes, C.M.M., Toop, L., Sluyter, J., Murphy, J., Khaw, K-T., Camargo, C.A. Jr. 2017. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the Vitamin D Assessment study : a randomized clinical trial. JAMA Cardiology 2: 608–16.

Smith, H., Anderson, F., Raphael, H., Maslin, P., Crozier, S., C Cooper, C. 2007. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women - a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology 46: 1852–57.