Daily *Versus* Single Dose Vitamin D Therapy in Children and Adolescents: How Good is the Evidence?

Source Citation: Tan JKG, Kearns P, Martin AC, Siafarikas A. Randomised controlled trial of daily versus stoss vitamin D therapy in Aboriginal children. J Paediatr Child Health. 2015;51:626-31.
Section Editor: Abhijeet Saha

Summary

In this randomized controlled trial (RCT), 43 participants having 25(OH) D level less than 78 nmol/L received daily or stoss vitamin D therapy with follow-up at 4–6 months and 9–12 months. Of these, 34 (79%) had insufficient (50–78 nmol/L) levels, 8 (19%) had mildly deficient (27.5–50 nmol/L) levels and 1 (2%) had deficient (<27.5 nmol/L) vitamin D level. Daily vitamin D therapy had a higher average increase in 25(OH) D levels from baseline than stoss therapy; however, this was not significant. The authors concluded that vitamin D insufficiency is common in Aboriginal children of Western Australia and stoss therapy is a safe alternative to daily vitamin D therapy, but requires further evaluation of timing and doses.

Commentaries

Evidence-based Medicine Viewpoint

Relevance: Recent years have witnessed an unprecedented interest in vitamin D status and potential impact of deficiency/insufficiency in health and various disease states. Initial studies focused on documenting population levels and establishing the proportion of people with levels below the conventional definitions of deficiency/insufficiency. Later investigations identified associations with various disease conditions including public health problems such as childhood pneumonia and iron deficiency anemia. More recently, investigations have focused on clinical benefits of therapeutic supplementation with vitamin D. These pieces of research have spawned further research in three different directions *viz* (*i*) focused investigations to identify plausible biologic mechanisms for pathologic effects of vitamin D deficiency; (*ii*) confirmation of therapeutic benefit of vitamin D supplementation in various clinical conditions; and (*iii*) replication of measurement of vitamin D levels in various population subgroups. A considerable body of recent research from India – both in children as well as adults – is also oriented in these directions [1-10]. These investigations are pertinent because despite the presence of abundant sunshine in India, high prevalence of vitamin D deficiency/ insufficiency is reported [11,12]. Against this background, the recent publication of a randomized controlled trial (RCT) conducted in Australian aboriginal children [13] provides an opportunity for a re-look at vitamin D related research.

Critical appraisal: The study [13] was initiated with a three-fold objective *viz* (*i*) reporting the status of vitamin D in Australian aboriginal children; (*ii*) comparison of vitamin D level among those residing in rural *vs* urban areas; and (*iii*) evaluating the efficacy of daily vitamin D supplementation *vs* stoss therapy in those with low levels. Stoss therapy refers to single high dose oral administration of vitamin D. Such a regimen is expected to reduce costs and improve compliance in comparison to daily administration of a similar total dose [14]. The investigators chose to conduct the study in aboriginal children anticipating greater risk of deficiency in them (on account of higher melanin content in skin). Accordingly, they enrolled aboriginal children and adolescents (<16 y) who were admitted in two health-care settings (representing rural and urban areas). The authors clearly reported the latitude of the geographic location of the two sites; unfortunately these differed by over 14 degrees raising the possibility of a completely different pattern of sun exposure. It is unclear why such an obvious confounding factor was overlooked.

The investigators failed to calculate the appropriate sample size required for their first two objectives. Instead, they merely stated that 40 children would be required for detecting a statistically significant difference in vitamin D level in the two therapeutic arms (daily therapy *vs* stoss therapy). Interestingly, even this limited sample size was not achieved even at the start of the therapy component of this study.

Methodology for the first two objectives has not been described. It is unclear whether consecutive children were enrolled, or a sampling framework to minimize selection bias was applied. Similarly, there was no effort to ensure matching of children enrolled from the rural and urban areas. These glaring omissions create serious risk of bias compromising the validity of the study. It almost appears as though the investigators were unconcerned about the first two objectives of the study. The third objective was approached through a RCT; wherein a computer was used to generate a block randomization sequence. Sealed envelopes were also used, although they were white (perhaps not opaque); hence the adequacy of allocation concealment cannot be judged. There was no blinding of participants; further, it appears that even the laboratory personnel testing the samples were unblinded. These also raise the risk of bias in this component of the study.

The authors stated that their primary outcome was vitamin D level at three points *viz* baseline, 4-6 months, and 8-12 months after initiating therapy. Unfortunately it is unclear which time-point was used to calculate the sample size. Further these time points are presented somewhat differently in the flow diagram (6 weeks, 6 months, 12 months) and in the 'Discussion' section (4-8 months and 8-12 months). Strangely, these discrepancies have been missed by the authors as well as the review/ editorial process.

On the plus side, the definitions of vitamin D deficiency (<50 nmol/L equivalent to 20 ng/ml) and insufficiency (50-78 nmol/L equivalent to 20-31.2 ng/ mL) conform to generally accepted standards. In contrast, the dosage of vitamin D chosen for stoss therapy in this trial (100,000 U) is lower than that used in other studies; the reason for this has not been described. However, children with severe deficiency (vitamin D less than 27.5 nmol/L or 11 ng/mL) received twice the dose as those with levels between 27.5 and 78 nmol/L.

Among 304 potentially eligible children, only 73 were evaluated for 25(OH) D levels. Of the 231 excluded children, 23 (10%) missed recruitment (no specific reason given). Of 43 children eligible to enter the RCT, only 37 were actually enrolled (thus the sample size was not achieved). Among these 37, only 6 were available for the final outcome measurement. This significant selection and attrition bias further compromises validity.

Although the serious threats to validity make it inappropriate to explore the results, these are briefly described for academic purposes. Overall, almost 60% of the children were found to have low vitamin D levels despite relatively high skin phototype (median score 5 in a scale where the highest is 6). It may be speculated that this is more-or-less as would be expected. Children from the rural area had higher vitamin D level, although the small sample size (only 12 in the rural group) makes it difficult to be confident of this interpretation. Although samples sizes are very small, it appears that vitamin D level did not vary by skin phototype. As mentioned, only 37 of 43 eligible participants were randomized to daily or stoss vitamin D therapy; of these, only 16 and 6 were available for the first and second follow-up measurements. The reasons for failure to randomize all eligible children, and follow them up per protocol have not been described. In the limited cohort available, it appears that daily therapy resulted in a higher mean increase in vitamin D levels.

The authors of this RCT recognized and acknowledged some of the limitations described above. Despite these limitations, and their own observation suggesting daily therapy yielded higher increase in vitamin D, they suggest that stoss therapy could be a useful option to treat vitamin D deficiency/insufficiency. It must be emphasized that such an interpretation from the methodology used and data available, is inappropriate, and at high risk of bias.

Extendibility: The serious limitations in the execution and outcomes of this study preclude an exploration of generalizability of results. Despite this, some lessons can be learnt for the Indian setting, especially as 25 (OH) D measurement is relatively easy and affordable in most research settings. Investigators must resist the temptation of undertaking a poorly planned study measuring 25 (OH) D levels in cohorts of children/adults (healthy or otherwise). When such studies are already available, their results must be interpreted with caution. Further, India is a geographically and ethnically diverse country; hence exposure to sunlight, UV index, population phototypes, etc can differ markedly even in populations/regions appearing to have common parameters. This makes extrapolation of results from one setting to other settings somewhat complicated. Last but not the least, there is ample data suggesting that the majority of people (healthy state or with various diseases) have low vitamin D levels (as per the conventional definitions). Therefore, further research must focus on biologic implications of this, and/or management strategies – rather than merely confirming/replicating existing data.

Conclusions: This study highlights several deficiencies in terms of research methodology and data interpretation. No applicable conclusions can be confidently drawn for our setting.

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Nutritionist's Viewpoint

As the number of related articles that have been submitted to Indian Pediatrics attest to, over the last two decades vitamin D physiology, its actions and role in disease have become the flavors of the month in many parts of the world, resulting in vitamin D status being assessed in numerous different groups, communities and populations. In a number of these, rickets remains a public health problem; thus an assessment of vitamin D status in these at-risk communities might be warranted, but in the greater proportion of communities, it is hard to understand why there should be concern about vitamin D status at all. So it possibly is with the Aboriginal children in Western Australia. I am sure the authors of the article would argue that the experimental evidence showing vitamin D being involved in numerous different functions and thus possibly affecting the well-being of those with longstanding low vitamin D status, warrants determining the vitamin D status of this group. But do we know what level of 25-hydroxyvitamin D [25(OH)D] constitutes vitamin D deficiency? I certainly would be very cautious about using the cut-offs indicated by the authors to diagnose vitamin D insufficiency or deficiency that requires management, until we have much firmer prospective evidence that children are at-risk when levels of 25-hydroxyvitamin D are between 30 and 50 nmol/L (12-20 ng/mL). I believe the recommendations made by the Institute of Medicine [1] which indicate that the risk of clinical vitamin D deficiency increases below 30 nmol/L, remain appropriate currently. The authors of the current pilot study suggest that the results obtained on the small number of children warrant the screening of Aboriginal children attending hospitals and clinics, and that daily supplements should be used for initial treatment; yet only 1 subject had a 25(OH)D value of <27.5 nmol/L. From my perspective, the data presented indicate that healthy Aboriginal children are not at risk of vitamin D deficiency and therefore do not warrant screening.

One of the original aims of the study was to determine the effectiveness of oral stoss therapy compared to daily supplements in improving vitamin D status; however due to the small number of children who returned for follow up, a meaningful comparison could not be made. However, the study does raise two issues: *(i*) when does one assess the effectiveness of stoss therapy in improving vitamin D status, as serum 25(OH)D levels are not constant but rise and then fall over several months; and *(ii)* how often should the bolus of vitamin D be given and does the interval change depending on the amount of vitamin D in the bolus and the size/age of the subject? In a study conducted in healthy adult women, an oral bolus of vitamin D_3 (150,000 IU) resulted in a rise in 25(OH)D which peaked between days 7 and 14, and had started to fall by day 28. Of interest was the change in serum vitamin D levels themselves, which were maximal on day 1 and back to baseline values by day 14 [2].

In conclusion, the study does not convince me to change my current practice but it does raise questions about the frequency and dosage required for stoss therapy. Until we have more understanding of the changes in mineral and vitamin D homeostasis that occur with stoss therapy, especially within the first two weeks of dosing, I will continue where possible to use daily therapy to correct vitamin D deficiency and to maintain sufficiency when necessary.

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Pediatrician's Viewpoint

Published under the category of 'Original Article' in a peer-reviewed indexed journal with impact factor of 1.19, this study is a classic example of misleading the science by posting conclusions that are neither backed by a sound hypothesis nor derived from an appropriate methodology. Authors conclude that vitamin D insufficiency is common in Aboriginal children of Western Australia. One would be surprised to know that this conclusion is drawn on the basis of an opportunistic sample of only 78 children, arbitrarily picked from hospitalized patients. The mean 25(OH)D level in study population was 74.5 nmol/L (95% CI 68.8,80.3), just a shade below the 78 nmol/L cut-off, assumed for defining insufficiency. Authors have grossly extrapolated these borderline results obtained on a cohort of sick children (inpatients) to the entire Australian Aboriginal community. This is unacceptable.

The study further, in a randomized controlled design, compares daily *vs.* Stoss regimen in these vitamin D insufficient children. The intervention is based on the premise that therapeutic vitamin D supplementation is needed in all subjects with insufficient vitamin D status, irrespective of whether they are symptomatic or not. Bolus/long-term vitamin D supplementation was originally developed to treat rickets (manifest vitamin D deficiency), but should it be used to correct isolated biochemical deficiency, is still open to debate. It is also to be noted that of 43 participants with low 25(OH)D levels (<78 nmol/L), who were given vitamin D therapy, only 9 were really deficient [25(OH)D <50 nmol/L]. No specific mention is there to monitor for hypercalcemia, hypercalciuria, pseudotumor cerebri, hypertension or nephrolithiasis. Statistical analysis is also faulty, with parametric tests used on a small sample size (without even testing for normality of data). To add, the final comparison of outcome data is based on only 14 and 6 children at different times point. More than half were lost to follow-up. Sufficient to say that the present study does not have any value for translation into policy or recommendation for practice.

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