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Original Research Article

A study on efficacy of low dose vitamin d regimen in the treatment of nutritional rickets

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Abstract

Introduction: Vitamin D deficiency is one of the most common nutritional deficiencies in the world with approximately one billion people at risk. It is on the rise in developed countries, even in Australia where there is an abundance of sunlight. Additional risk factors among newly settled refugees include veiling, dietary deficiencies, darker skin colour and unfamiliarity with the local healthcare system. More specifically, in Australian children with vitamin D deficiency rickets, risk factors include dark skin and maternal veiling with 96-98% of these being children migrants or born to a migrant parent.
Materials & Methods: This study was conducted in a tertiary centre, of Karnataka, India., randomized controlled study was conducted at a tertiary care, between Jan 2018 and Dec 2019. We aimed to compare the efficacy of daily vs. low dose depot oral vitamin D3 for treating nutritional rickets. We conducted a randomised controlled trial in the department of paediatrics of a tertiary care hospital catering to semi-urban and rural population in Karnataka, India. We randomised 30 children, aged 3 months to 5 years with nutritional rickets to receive either daily oral vitamin D3 drops (3-12 months: 2000 IU; > 12 months to 5 years: 4000 IU; n 33) for 12 weeks duration or a single oral depot dose of vitamin D3 granules (3-12 months: 60 000 IU; > 12 months to 5 years: 150 000 IU; n 33). Participants in both groups had comparable demographic characteristics, laboratory features and radiological severity of rickets.
Results: 15 participants in each group received the assigned intervention and all were followed up till 12 weeks. At 12 weeks follow-up, children in both groups showed a significant improvement in all biochemical parameters (serum Ca, P, alkaline phosphatase (ALP), parathormone and 25(OH) vitamin D levels) as well as radiological healing. At 12 weeks, the mean serum 25(OH) vitamin D levels (nmol/l) were statistically comparable in both groups (daily: 120·2 (sd 83·2), depot: 108 (sd 74), P = 0·43) and 31 (93·9%) children in each group had radiological healing (Thacher score < 1·5). Two children in each group persisted to have raised ALP and one child each in the daily group continued to have hypocalcaemia and hypophosphataemia at 12 weeks.
Conclusion: Low dose oral depot vitamin D3 is an effective alternative to daily oral vitamin D3 for nutritional rickets.

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Introduction

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.
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. These investigations are pertinent because despite the presence of abundant sunshine in India, high prevalence of vitamin D deficiency/insufficiency is reported. Against this background, the recent publication of a randomized controlled trial (RCT) conducted in Australian aboriginal children provides an opportunity for a re-look at vitamin D related research. Vitamin D is involved in the regulation of several skeletal and non-skeletal functions through the action of its active metabolite, $1,25(OH)_2D$. Research into non-skeletal effects of vitamin D has increased greatly in recent years. Some of these associations include suppression of proliferation and differentiation of cancer cells, modulation of innate and adaptive immunity, modulation of muscle cell proliferation, improved cardiovascular health, modulation of pancreatic beta cell function and insulin sensitivity, clearance of amyloid plaques and promotion of survival, development and neuron function. Furthermore, low vitamin D concentrations have been associated with increased longitudinal risk of hypertension, diabetes, cardiovascular disease and atherosclerosis.

Vitamin D deficiency, whilst prevalent, is often asymptomatic. Clinical features include rickets, craniotabes, bone pain, muscle pain, hypocalcemic seizures, delayed gross motor milestones and irritability, but more compared to older children and adolescents.

Increasing sunlight exposure within recommendations for the prevention of skin cancer is the ideal method of improving vitamin D status, but it may not be suitable or effective for refugee children due to darker skin colour, veiling and other socio-cultural factors. A recent international consensus paper recommends implementing national supplementation and fortification of food programmes with vitamin D and/or calcium to address the high rates of nutritional deficiency. For high risk ethnic groups, vitamin D supplementation during every winter and spring has been suggested.

Due to the longer periods of treatment required in this group, adherence with daily oral vitamin D supplementation is problematic and hence, depot (or "stoss") vitamin D supplementation at larger doses in intervals of weeks or months may be a suitable alternative therapeutic option. The use of high-dose depot vitamin D therapy is increasing, but there are little data on its use in children. In Australia, the experience with depot vitamin D therapy is limited.

Materials & Methods

We randomised 30 children, aged 3 months to 5 years with nutritional rickets to receive either

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daily oral vitamin D3 drops (3-12 months: 2000 IU; > 12 months to 5 years: 4000 IU; n 33) for 12 weeks duration or a single oral depot dose of vitamin D3 granules (3-12 months: 60 000 IU; > 12 months to 5 years: 150 000 IU; n 33). Participants in both groups had comparable demographic characteristics, laboratory features and radiological severity of rickets. This study was conducted in a tertiary centre, of Karnataka, India., randomized controlled study was conducted at a tertiary care, between Jan 2018 and Dec 2019.

Search strategy

The protocol used was based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The methodology implemented in this systematic review and meta-regression study was in accordance with the general methods in the Cochrane group guidelines. A comprehensive literature search was conducted in databases including Embase, PubMed, Cochrane library, Popline and Global Index Medicus without language restriction. MeSH terms and keywords related to Vit D and RCT were applied. Additional trials were identified by searching trial registries, including the WHO International Clinical Trials Registry (ICTRP) and the Clinical Trials.gov and the references lists of recent systematic reviews on Vit D trials were also screened.

Data extraction and quality assessment

A data extraction record form was prepared and used to document the key information, intervention details (type of Vit D use, dose, frequency, start time/season and end time/season, duration), concomitant calcium supplementation or not, number of participants per arm, age, BMI, baseline and post-intervention 25(OH) D concentration and assay method was identified. Corresponding means and standard deviations (SDs) of each arm were also extracted. Other statistical variable data like median and interquartile range (IQR) were converted to means and SDs. For studies with large sample and data of symmetric distribution, the median is very similar to the mean and the width of the quartile spacing is about 1.35 times of SD. For studies with small sample size or data of asymmetric distribution, several formulas were used to estimate the mean and SD for different sample size from median, range and IQR. The Jadad scale was used to assess the quality of included studies in three domains (randomization, blinding and withdrawals and dropouts).

Covariates assessment

Covariates were assessed by the following methods: season was divided into five categories according to changes in sunshine intensity from abundance to scarcity and from scarcity to abundance for of both the season of starting and ending the supplementation. If the study started and ended in seasons with abundant sunshine (summer and autumn), they were assigned a value of "1"; for studies carried out from abundant to inadequate sunshine, "2", from inadequate to abundant sunshine, "3" and from inadequate to inadequate, "4". With missing data, either for season of starting, stopping or both, they assigned a "5". For supplementation frequency, the assigned value for "daily" was "1" and others, "0". Concomitant Ca supplementation was assigned "1", whereas no Ca supplementation was "0". Latitude was classified into three classes of low ([less than or equal to]23.5°), medium (23.5°-40°) and high ([greater than or equal to]40°). For pregnant women, the gestational stage at which supplementation began and ended were noted using the relevant trimester. Producing five categories [first trimester to delivery, second to third trimester, second trimester to delivery, second trimester to postpartum and third trimester to delivery], numbered "1" to "5", respectively. 25(OH)D concentrations that were reported in ng/mL were transformed into nmol/L [1 ng/mL = 4 nmol/L] and Vit D dose was recorded as IU according to IOM usage.

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Full-text references for inclusion, data extraction and quality assessment were screened.

Statistical analysis

We conducted a random meta-analysis with at least two studies included in each population for the outcome of post-intervention 25(OH)D concentration. Weighted mean difference (WMD) and 95% confidence interval (CI) were calculated and presented as forest plots. The heterogeneity between studies was assessed using I^2. The degree of heterogeneity was classified as low (I^2 < 25%), moderate (I^2 25-75%) or high (I^2 > 75%), respectively. For comparison purposes, we calculated the weighted mean (WM) of the Vit D dose and 25(OH)D concentrations for different dosage groups.

Discussion

We found that oral low dose depot of vitamin D3 (60,000 IU in children aged 3-12 months and 150,000 IU in children aged 1-5 years) is an effective and safe alternative to daily oral vitamin D3 given for 12 weeks' duration for treating nutritional rickets in < 5 years age children without any increased risk of hypercalcemia. Both the regimens achieved comparable clinical, biochemical and radiological resolution without any adverse effects of therapy.

At 4 weeks follow up, we found that both groups showed significant rise in serum calcium and phosphorus and fall in serum alkaline phosphatase; the serum phosphorus levels being significantly higher in the depot group compared to daily group. At 12 weeks, however, the serum phosphorus was comparable in both treatment groups and hence this early rise in serum phosphorus in the depot group may be of little clinical benefit. The increase in mean serum 25(OH)D levels was comparable in both groups despite the fact that the cumulative vitamin D3 dose in the daily group is twice that in the depot group. A subgroup analysis of the effect of the two treatment strategies in vitamin D deficient children with rickets, showed that both regimes were equally effective in terms of biochemical and radiological resolution of rickets as well as increase in serum 25(OH)D levels. In contrast, another study has shown that in vitamin D deficient children, daily oral vitamin D3 supplements have fared better than low dose oral depot (100,000-200,000 IU) vitamin D3 doses in achieving and maintaining normalcy in serum vitamin D levels, although they increase the risk for hypervitaminosis D and hypercalcemia.

We found that 2 children in the daily group developed hypervitaminosis D and 1 child in the depot group developed hypervitaminosis D, although these children were asymptomatic and without concomitant hypercalcemia. Similar observations have been reported previously with the use of low dose oral vitamin D bolus in rickets. None of the children in either groups had serum 25(OH)D levels exceeding 352 mmol/l reiterating the safety of both regimes. No child developed hypercalcemia in either groups. Previously, hypercalcemia was shown to be more likely with the use of higher oral depot doses of vitamin D (600,000 IU and 300,000 IU) compared to low dose (150,000 IU) oral vitamin D bolus. We found that four children (two per group) had TS ≥ 1.5 at the end of 12 weeks which might suggest the need for continued supplementation of vitamin D3 and calcium beyond 12 weeks in rickets. Contrasting to our figures of 91%, Chatterjee, *et al*. (21) showed that only 47% of children with rickets who received 600,000 IU of D3 had TS of 0 after 12 weeks in rickets. This emphasizes that radiological healing may take more than 12 weeks and continued therapy may be needed in a few cases of rickets. The strengths of our study include a head-to-head comparison of a single low dose depot oral vitamin D3 with daily vitamin D3 therapy. A comprehensive assessment of clinical, biochemical and radiological parameters in a homogenous cohort empowers our

study. A robust follow up and good compliance by all participants was possible in our study as one of the research team members was dedicated to carrying out follow up. Limitations of our study include the fact that we did not estimate hypercalciuria, another marker of safety profile of vitamin D supplementation. Only 23% of our participants were aged ≤ 12 months and hence focused studies on infants evaluating efficacy of these regimens would be preferred. A prolonged follow up at 6-12 months post-treatment would be preferred to assess complete radiological resolution in the children with less than complete healing at 12 weeks and whether serum 25(OH)D sufficiency is sustained in the children post treatment.

Results

15 participants in each group received the assigned intervention and all were followed up till 12 weeks. At 12 weeks follow-up, children in both groups showed a significant improvement in all biochemical parameters (serum Ca, P, alkaline phosphatase (ALP), parathormone and 25(OH) vitamin D levels) as well as radiological healing. At 12 weeks, the mean serum 25(OH) vitamin D levels (nmol/l) were statistically comparable in both groups (daily: 120·2 (sd 83·2), depot: 108 (sd 74), P = 0·43) and 31 (93·9%) children in each group had radiological healing (Thacher score < 1·5). Two children in each group persisted to have raised ALP and one child each in the daily group continued to have hypocalcaemia and hypophosphataemia at 12 weeks.

Summary

In this randomized controlled trial (RCT), 30 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, (79%) had insufficient (50-78 nmol/L) levels, (19%) had mildly deficient (27.5-50 nmol/L) levels and (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 children of India and stoss therapy is a safe alternative to daily vitamin D therapy, but requires further evaluation of timing and doses.

Conclusion

Sunlight is the major determinant of vitamin D stores in our population. Neither variation in skin type within Caucasians nor diet modified this association to any significant extent. Extrapolation of these findings to sunlight bone mass associations in a very similar population suggests that a minimum level of around 50 nmol/l in the population is required for optimal bone development in prepubertal children but this needs to be confirmed with further controlled trials of vitamin D supplementation and bone mass. A low dose oral depot vitamin D3 is an effective regimen to treat nutritional rickets in under-5 children. Compared to the daily oral vitamin D3 regimen, it offers the advantage of convenience and ease of administration.

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