Original Article

Efficacy and Safety of 90,000 IU versus 300,000 IU Single Dose Oral Vitamin D in Nutritional Rickets: A Randomized Controlled Trial

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Abstract

Aim: To compare efficacy and safety of 90,000 IU versus 300,000 IU oral single dose vitamin D for treatment of nutritional rickets. **Study Design:** Randomized controlled trial. **Setting:** Tertiary care hospital. **Participants:** One hundred ten children (6 months to 5 years, median age 10.5 months) with rickets. Exclusion criteria were disease affecting absorption, intake of calcium/vitamin D preparation in last 6 months, abnormal renal function, and rickets other than nutritional. **Intervention:** Vitamin D3 as a single oral dose 90,000 IU (group A, $n = 55$) or 300,000 IU (group B, $n = 55$). **Methodology:** Severity of rickets was scored on knee and wrist X-ray as per Thacher's radiographic score. Baseline serum levels of calcium, SAP, 25(OH)D, iPTH were measured. Follow up was done at 1 week, 4 weeks, and 12 weeks. **Outcome Variable:** Primary – Radiographic score at 3 months. Secondary – Serum levels of 25(OH)D, SAP, and iPTH at 3 months, clinical and biochemical adverse effects. **Results:** Eighty-six subjects (43 in each group) completed the study. The radiographic score reduced from 6.90 to 0.16 in group A and from 6.93 to 0.23 in group B. The levels of 25(OH)D, ALP, and PTH were similar between the groups at baseline and follow up. Hypercalciuria and hypercalcemia were seen more often in group B as was hypervitaminosis D. There were no clinical adverse events. **Conclusions:** Single oral dose vitamin D3 90,000 IU is safe and effective in achieving healing of rickets.

Keywords: Nutritional rickets, radiographic score, vitamin D

INTRODUCTION

Nutritional rickets is a worldwide health concern caused by deficiency of vitamin D and/or calcium.[1,2] Though the treatment seems simply to replace vitamin D and calcium, there is wide variation in the practiced treatment world over. Over the past some years, the treatment modalities have changed considerably. Not many years ago, the standard practice among pediatricians was to use single intramuscular doses of 600,000 IU.[3] Subsequently, single day large oral doses of vitamin D were demonstrated to be safe and effective while avoiding the complications of parenteral route.[4] With accumulating evidence favoring smaller doses and oral route, 300,000 IU is being regarded as a good therapeutic dose.[5] The lower doses have demonstrated adequate biochemical and radiological healing without hypercalcemia or hypercalciuria that are seen with higher doses. A Turkish study by Cesur *et al.* compared the effects of 150,000 IU, 300,000 IU, and

600,000 IU of oral vitamin D in 56 infants and toddlers and reported no difference in radiological improvement among the three doses, but 2/28 in the 300,000 IU group and 6/28 in the 600,000 IU group developed hypercalcemia at 4 weeks, albeit asymptomatic.[6] Similarly, another study comparing effects of 300,000 IU versus 600,000 IU oral vitamin D in 76 children with nutritional rickets, reported good radiological healing with both the doses, but hypercalcemia was observed in 3/32 of 300,000 IU dose group and 2/28 in 600,000 IU group at the end of 12 weeks.[7]

The global consensus guidelines have advocated small daily doses of 1000–2000 IU for 2–3 months in infants and children.[1]

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However, compliance may become compromised with no additional benefit in either efficacy or safety profile. There is also evidence to prove that it is the total dose that affects outcome rather than the period over which it is administered.[8] Moreover, the cost of daily therapy is considerably more in countries like ours.[2]

Hence, we planned to study and compare the safety and efficacy of single oral dose of 90,000 IU vitamin D with 300,000 IU single oral dose in the treatment of nutritional rickets in children.

MATERIALS AND METHODS

The study was conducted in the Department of Pediatrics of a tertiary care center of North India after clearance from the institutional ethics committee and with due written informed consent from parents/guardians.

Participant selection

Subjects were recruited from pediatric outpatient clinic as well as admitted patients from pediatric wards. Children in the age group of 6 months to 5 years, suspected to have rickets (on the basis of clinical features) were offered participation in the study. After signed informed consent from the parents, all participants underwent detailed clinical examination followed by blood samples and X-rays both hands and knees antero-posterior view.

All subjects, who were found to have radiological rickets with Thacher's score >1.5, were randomized to receive one of the two intervention doses of vitamin D along with equal dose of calcium supplementation (50 mg/kg body weight). Randomization was done on the basis of 1:1 subjects in both the groups (random table generated from www.randomization. com). Any subject already diagnosed with any disease affecting absorption or taking oral steroids, antitubercular, or antiepileptic drugs were excluded from the study. Similarly, participants who had taken or taking calcium or vitamin D supplementation in last 6 months were excluded from the study. After biochemical screening, additional exclusion criteria applied were presence of abnormal renal function for age. Similarly, subjects with suspicion of other than nutritional cause of rickets were also excluded.

Sample size

Sample size was calculated according to two group test of equivalence in proportions and assuming expected difference of proportion as 0.04 for radiological healing at 12 weeks, based on results of a previous study by Soliman *et al*.[9] Keeping the α as 0.05 and power as 80% and adding 20% lost to follow up, a sample size of 55 in each arm was considered adequate.

Data collection

The selected subjects were evaluated and data entered in a pre-structured working proforma. This included a detailed clinical history and physical examination. Height (length if child was <2 years) and weight were recorded as per standard
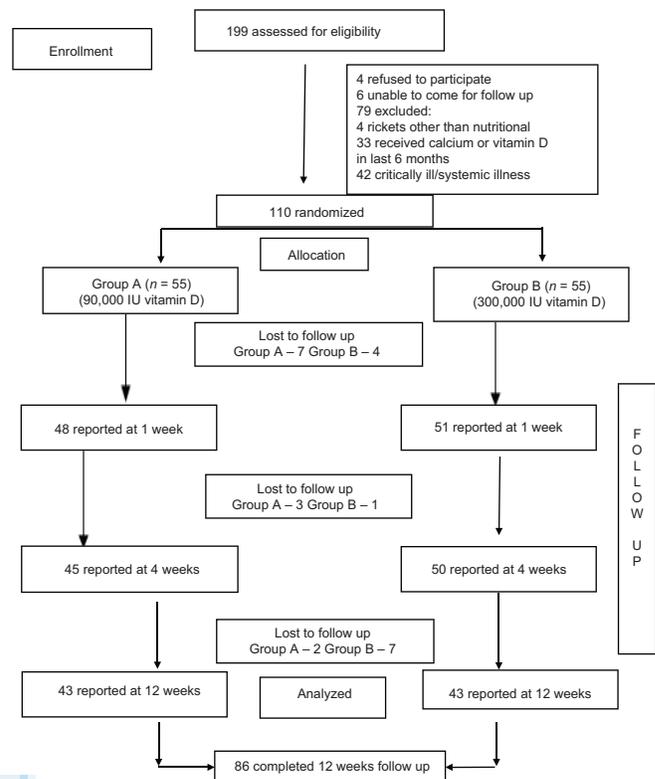

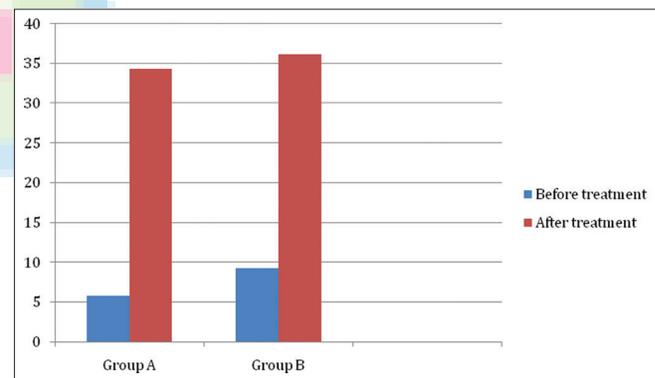**Figure 1:** Study CONSORT flow diagram

Figure 2: Comparison of mean serum 25(OH)D levels (in ng/mL) between the two groups before and after treatment
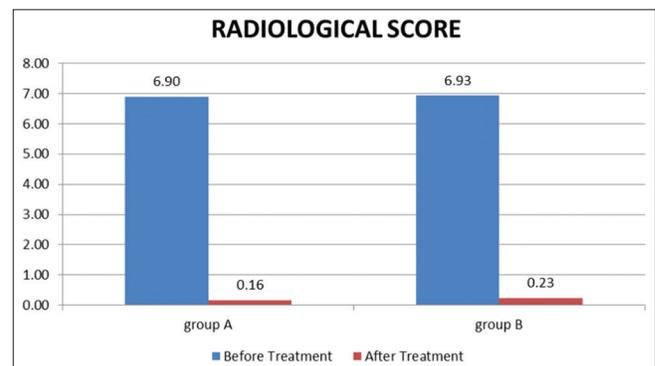

Figure 3: Comparison of mean radiological score in the two groups before and after treatment

techniques with the World Health Organization (WHO) growth standards as reference population.[10] X-rays of the wrists and knees were obtained for all enrolled subjects and scored as per Thacher's radiological scoring (on a scale of 0–10) for rickets by a radiologist blinded to the treatment allocation.[11] Venous blood sample was obtained for estimation of renal functions, serum albumin, calcium, phosphate, alkaline phosphatase (SAP), and serum levels of 25 hydroxy vitamin D [25(OH)D] and intact parathyroid hormone (iPTH). Serum 25(OH)D was measured on the DiaSorin auto analyzer ('LIASON'DiaSorin, Inc., Stillwater, MN, USA) using a chemiluminescent label. The reproducibility of the assay ranged from 6% to 12% and was within the performance characteristics described by the manufacturer. Our laboratory is registered with the UK-DEQAS vitamin D assay external quality control assessment program and hence met their performance targets regularly (www. deqas. org). Serum intact parathormone was measured by immunoenzymatic assay using a chemiluminescent label on ACCESS-2 Beckman Coulter (total imprecision <12% at concentrations >12 pg/mL).

Hypocalcemia was defined as serum calcium <8.8 mg/dL and hypercalcemia as >10.8 mg/dL.[12] Serum phosphate <3.8 was considered as hypophosphatemia.[12] Serum 25(OH)D was classified as being <20, between 20 to 30 and >30 ng/mL while levels >150 ng/mL were considered as hypervitaminosis D.[13] Serum iPTH >65 pg/mL was considered to be elevated. Cut-offs for hypercalciuria were defined as per age-related values of urine calcium/creatinine ratio established by Metz.[14]

Randomization and intervention

Patients were allocated to one of two treatment arms according to web-generated sequence using block randomization (block sizes of 10, 8, and 4). The sequence was transcribed to sequentially numbered opaque sealed envelopes by a person not directly involved in the study. Group A received 90,000 IU vitamin D, single oral dose while group B received 300,000 IU vitamin D, single oral dose. The selected formulation was in tablets of strength 60,000 IU and rated most appropriate (actually containing the mentioned composition) as per a previous study by Khadgawat *et al*.[15] The preparation was dissolved in 30 mL of milk and administered to the subject under direct supervision of the investigator. For obtaining half tablet dose (required in group A), the full tablet was dissolved in 5 mL milk and 2.5 mL drawn from that. Both the groups received calcium supplements at 50 mg/kg/day for 90 days starting from the day of intervention. The supplement was specially manufactured so as not to contain any vitamin D. Those with hypocalcemic seizures received injectable calcium gluconate as per departmental protocol and later oral calcium as per study protocol.

Follow up

The subjects were called for follow up between 7th to 10th day, 30th to 37th day, and 90th to 97th day after intervention. A reminder card was given and telephonic calls were made to ensure the follow-up visits. At each visit, 5 mL of urine was collected for measuring urine calcium/creatinine ratio

and any symptoms related to hypercalcemia (headache, abdominal pain, nausea, vomiting, and constipation), during the intervening period, were enquired for. At second follow up, serum calcium, phosphate, SAP were measured, while at third and final follow up, serum calcium, phosphate, SAP, 25(OH)D, and iPTH were measured along with urinary calcium/creatinine ratio, and X-rays of the wrists and knees. Radiological changes were scored by the same radiologist who was blinded for intervention.

Outcome variable

The primary outcome variable was radiographic score at third visit, 90th to 97th day after intervention. The secondary outcome variables were symptoms related to hypercalcemia, urine calcium/creatinine ratio, increase in 25(OH)D, and decline in serum iPTH and SAP at 90 days.

Statistical analysis

Continuous variables were expressed as mean and compared using the unpaired *t*-test, whereas Mann–Whitney U test was used for variables not normally distributed. Categorical variables were expressed as absolute numbers and percentages and compared using a Chi-square test or the Fisher's exact test. The Spearman's correlation was used to correlate SAP, iPTH, 25(OH)D, and other biochemical parameters with the radiographic score. For all statistical tests, a *P* value <0.05 was considered significant. SPSS Statistics for Windows, Version 17.0. (SPSS Inc., Chicago), was used for statistical analysis.

RESULTS

Of the 199 subjects eligible for inclusion, 79 were excluded (4 were rickets other than nutritional, 33 had received calcium or vitamin D in last 6 months, and 42 were critically ill or had systemic illness), 4 refused to participate, and 6 expressed inability to come for follow up. The 110 patients thus selected were randomized to receive either 90,000 IU oral vitamin D (group A) or 300,000 IU oral vitamin D (group B). By the end of 90 days, 12 patients were lost to follow up in each group as shown in Figure 1.

The mean age of the study population was 10.5 months, 44 were females (40%) and 66 were males (60%). The most common presenting complaint was seizures (50%) followed by lower respiratory tract infection (23.6%), bony deformities in 16.4%, delayed milestones in 6.4%, and severe acute malnutrition in 2.7%. The biochemical parameters are shown in Table 1. Hypocalcemia was present in 79 (71.8%), hypophosphatemia in 63 (57.2%), and raised SAP in 109 (99.09%). Serum 25(OH)D was <20 ng/mL in 95 (86.3%), between 21 to <30 ng/mL in 2 (1.8%), and >30 ng/mL in 4 children. Serum iPTH was elevated in 103 patients (93.6%). The radiographic score was 1–4 in 23 (20.9%), 5–8 in 71 (64.5%), and >8 in 16 (14.5%). The mean radiographic score was 6.9 (group A – 6.9, group B – 6.93) and 14.5% patients had a score of 10. The group wise scores are shown in Table 2.

Table 1: Baseline biochemical parameters in the two groups

Variable	Group A		Group B		P
	Mean±SD	Median	Mean±SD	Median	
Serum calcium (mg/dL)	7.99±1.52	8.23	7.50±1.54	7.8	0.093
Serum phosphate (mg/dL)	3.58±1.20	3.50	3.64±1.47	3.45	0.914
SAP (IU/L)	974.64±438.24	860	989.40±390.78	945	0.564
Serum 25(OH)D (ng/mL)	5.78±10.11	3.50	9.23±19.71	3.7	0.405
Serum iPTH (pg/mL)	302.95±212.26	243	246.49±134.37	225.3	0.285

SAP: Serum alkaline phosphatase, iPTH: Intact parathormone, SD: Standard deviation, 25(OH)D: 25 hydroxy vitamin D

Table 2: Baseline radiographic scores in the two groups

	Group A, *n* (%)	Group B, *n* (%)
Mild (<4)	11 (20)	12 (21.8)
Moderate (4-8)	37 (67.3)	34 (61.8)
Severe (>8)	7 (12.7)	9 (16.4)
Total	55 (100)	55 (100)

P=0.81 for the groups

Follow up

At 1 week, 99 children came for follow up, of which 48 belonged to group A and 51 belonged to group B. No patient reported any symptom suggestive of hypercalcemia though there was hypercalciuria in three patients of group A and five of group B. At 4 weeks follow up, the serum calcium level had risen in both the groups and the levels were comparable. Likewise, the other biochemical parameters (SAP and iPTH) were statistically comparable. Hypercalcemia was seen in three patients in group A and two in group B, while hypercalciuria was seen in one subject in group A and two in group B.

At third follow-up visit at 12 weeks after intervention, the serum calcium levels normalized in 88.6% subjects in group A and in 90.69% subjects in group B. The mean levels are as shown in Table 3. SAP continued to be raised in 44.1% (19/43) in group A and in 32.5% (14/43) in group B. Serum 25(OH)D levels increased to >20 ng/mL in 73.6% of group A and 77.4% of group B. In two subjects in group B, it increased to >150 ng/mL while none of group A had such levels. Figure 2 depicts the mean improvement in S. 25(OH)D levels in the two groups. There was hypercalcemia in three subjects in each group and hypercalciuria in one of each group.

X-rays of both hands and knees were obtained again at this visit and scored by a radiologist. Complete healing (score reduced to zero) was seen in 90.7% subjects in group A and 90.7% in group B. In seven subjects who did not show complete healing, the rickets score had shown significant improvement from the baseline and had reduced to <4. Only one case had rickets scoring in the moderate range and he belonged to group B (300,000 IU) [Table 4]. The mean radiological scores in the two groups before and after treatment are compared in Figure 3.

Correlations

A significant correlation between SAP and radiographic score was found at baseline but not at 12 weeks.

There was no significant correlation between vitamin D, calcium, and iPTH in relation to radiographic score at baseline or at 12 weeks post treatment.

DISCUSSION

We conducted this study to establish the safety and efficacy of a lower dose (90,000 IU) of vitamin D in healing of rickets and found results comparable to 300,000 IU in efficacy and better in safety. Treatment of rickets, as given practically, has many variations as regards to route, dose, and the duration over which it is given. The oral route is well tolerated and effective. Doses could be given as daily dose over long duration or as a single dose therapy (stoss) that are advantageous in terms of improved compliance. Various dose regimens for treatment of rickets have been used by different studies.

Stögmann *et al*. compared stoss regime (400,000 IU vitamin D3, given as 200,000 IU orally on day 1 and day 3) versus continuous treatment (9,600 IU vitamin D3, daily for 18 days, cumulative dose of 172,800 IU) and found no difference between the two treatment groups.[16] In another study, three different therapeutic modes (single dose of 150,000 IU intramuscular, single dose of 150,000 IU orally, and oral 5,000 IU/day for 30 days) were compared, with similar improvement in rickets.[17] Similarly, Özkan *et al*. also evaluated the efficiency of three different therapeutic approaches (300,000 IU orally single dose, 300,000 IU intramuscular single dose, and 600,000 IU orally single dose of vitamin D), and found no difference in response to treatment among the groups.[18] However, the group that received 600,000 IU dose had 30% incidence of hypercalcemia. A study from Kuwait compared the efficacy of single intramuscular dose of vitamin D (600,000 IU) with that of an oral daily dose of vitamin D (2,000 IU) for 4 weeks in infants with nutritional rickets. Among those on oral therapy, 40% did not achieve radiographic healing and this was attributed to poor compliance.[19]

Cesur *et al*. did not find any difference among three doses of vitamin D (150,000 IU, 300,000 IU, and 600,000 IU as single oral dose) in the healing of rickets. However, hypercalcemia developed in eight infants, 2/20 who received 300,000 IU dose and 6/16 who received 600,000 IU dose.[6] Soliman *et al*. administered single dose of vitamin D in doses of 10,000 IU/kg intramuscular (upto a maximum of 150,000 IU) with radiographic evidence of complete

Table 3: Biochemical parameters in the two groups at 12 weeks after intervention

	Group A		Group B		*P*
	Mean±SD	Median	Mean±SD	Median	
Serum calcium (mg/dL)	9.72±0.74	9.60	9.99±0.63	9.9	0.034
Serum phosphate (mg/dL)	5.34±0.69	5.47	5.50±0.76	5.58	0.401
SAP (IU/L)	457±368.33	378.5	372.52±167.04	340	0.248
Serum 25(OH)D (ng/mL)	34.32±26.04	26.00	36.14±23.36	27.5	0.449
Serum iPTH (pg/mL)	37.08±12.88	35.84	46.98±36.79	42	0.151

SAP: Serum alkaline phosphatase, iPTH: Intact parathormone, SD: Standard deviation, 25(OH)D: 25 hydroxy vitamin D

Table 4: Radiographic scores in the two groups 12 weeks after intervention

	Group A, *n* (%)	Group B, *n* (%)
Zero	39 (90.7)	39 (90.7)
Mild (<4)	4 (09.1)	3 (07.0)
Moderate (4-8)	0	1 (02.3)
Severe (>8)	0	0

P=0.564 for the groups

healing in 95% subjects.[9] More recently, an Indian study evaluated the non-inferiority of 300,000 IU to 600,000 IU oral vitamin D (administered as single dose) and demonstrated radiologic healing in all subjects at 12 weeks. However, hypercalcemia was seen in 1/32 and in 1/34 at 4 weeks in the groups that received the lower and higher dose, respectively.[7]

Our results demonstrated that good healing of rickets can be achieved with 90,000 IU single oral dose of vitamin D without any increased risk of hypercalcemia and hypercalciuria. Hypercalcemia was noted in similar numbers of subjects in both the groups, however, none of them were symptomatic. Hypercalcemia is more likely to occur with higher doses of vitamin D as reported by Cesur *et al*.[6]

The higher dose (300,000 IU) also resulted in hypervitaminosis D [S.25(OH)D >150 ng/mL] in 2/43 subjects which was not seen in the group receiving 90,000 IU dose. Hypervitaminosis D is more likely with higher doses and our results also corroborate with that.[20]

The study, conducted as part of postgraduate thesis work, had a large number of inpatients and the most common presenting manifestation was hypocalcemic seizures. Similarly, hypocalcemia had a high incidence of 72% comparable to high incidences reported by other authors.[6,7] S.25(OH)D level <20 ng/mL was seen in the majority (86.3%) as also reported by other Indian authors.[7,21] In our study, four cases had S.25(OH)D level >30 ng/mL, however, all of them had rickets at the time of inclusion. It may be possible that they might have received vitamin D supplementation just before inclusion although we tried our best to obtain clear history of vitamin D supplementation at the time of inclusion. It may also be possible that calcium deficiency alone may be responsible for radiological features of rickets as also ascribed to by various authors.[21-23] All of these four patients showed complete radiological healing at the end of

study. Two patients of these four belonged to group A and the rest to group B. None of these subjects developed hypercalcemia or hypercalciuria. Their initial calcium ranged from 5.4 mg/dL to 8.7 mg/dL and this increased to 9 mg/dL–9.5 mg/dL.

The radiological response to the two different doses was similar with >90% patients showing complete healing with radiographic score reduced to zero at 12 weeks. This is in conformity with the results of other authors who have observed considerable improvement though the scores may not reduce to zero in all cases.[7,9,21]

Mittal *et al*., using single dose of 300,000 IU oral in group A and 600,000 IU oral in group B, demonstrated scores ≤4 at 12 weeks.[7] Similarly, Aggarwal *et al*. also observed reduction in radiological score to <1.5 in 70% of the subjects, who received high dose vitamin D (single dose 600,000 IU, intramuscular).[21]

In seven out of eight patients (group A – 4 and group B – 4) who did not show complete healing (radiographic score more than zero), score had shown significant improvement from the baseline and had reduced to <4 in six subjects. Only one patient with initial score of 10, had shown significant decrease in score, but remained in moderate range of score of 6. This subject belonged to group B (300,000 IU). It is very much possible that if we could have followed these children further, their score could have reduced to zero as shown by Chatterjee *et al*.[24] They demonstrated that initial radiographic score and radiological resolution were linearly associated and the time for radiographic score to be 0 had a mean of 126 days, ranging from 20 to 180 days.

The strengths of our study include a robust design, powered to assess radiologic healing of rickets and use of a validated vitamin D formulation that was administered under direct supervision. We used age appropriate cut-offs to define hypercalciuria. Our limitations were not being able to measure S.25(OH)D level at 4 weeks when more incidence of hypervitaminosis D could have been picked up. Also, a further follow up could have been done to assess the final healing in rickets especially in subjects who did not achieve radiographic score of zero at third follow up. Our study may form the basis of further research in larger number of patients and establish new guidelines.

Conclusions

We conclude that 90,000 IU vitamin D, single oral dose, is an effective as well as safe regimen for treatment of nutritional rickets in Indian children aged <5 years.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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