

300,000 IU or 600,000 IU of Oral Vitamin D3 for Treatment of Nutritional Rickets: A Randomized Controlled Trial

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Objective: To evaluate the non-inferiority of a lower therapeutic dose (300,000 IU) in comparison to standard dose (600,000) IU of Vitamin D for increasing serum 25(OH) D levels and achieving radiological recovery in nutritional rickets.

Design: Randomized, open-labeled, controlled trial.

Setting: Tertiary care hospital.

Participants: 76 children (median age 12 mo) with clinical and radiologically confirmed rickets.

Intervention: Oral vitamin D3 as 300,000 IU (Group 1; $n=38$) or 600,000 IU (Group 2; $n=38$) in a single day.

Outcome variables: Primary: Serum 25(OH)D, 12 weeks after administration of vitamin D3; Secondary: Radiological healing and serum parathormone at 12 weeks; and clinical and biochemical adverse effects.

Results: Serum 25(OH)D levels [geometric mean (95% CI)] increased significantly from baseline to 12 weeks after therapy in both the groups [Group 1: 7.58 (5.50–10.44) to 16.06 (12.71–20.29) ng/mL, $P<0.001$]; Group 2: 6.57 (4.66–9.25) to 17.60 (13.71–22.60, $P<0.001$). The adjusted ratio of geometric mean serum 25(OH)D levels at 12 weeks between the groups (taking

baseline value as co-variate) was 0.91 (95% CI: 0.65–1.29). Radiological healing occurred in all children by 12 weeks. Both groups demonstrated significant ($P<0.05$) and comparable fall in the serum parathormone and alkaline phosphatase levels at 12 weeks. Relative change [ratio of geometric mean (95% CI)] in serum PTH and alkaline phosphatase, 12 weeks after therapy, were 0.98 (0.7–1.47) and 0.92 (0.72–1.19), respectively. The serum 25(OH)D levels were deficient (<20 ng/mL) in 63% (38/60) children after 12 weeks of intervention [Group 1: 20/32 (62.5%); Group 2: 18/28 (64.3%)]. No major clinical adverse effects were noticed in any of the children. Hypercalcemia was documented in 2 children at 4 weeks (1 in each Group) and 3 children at 12 weeks (1 in Group 1 and 2 in Group 2). None of the participants had hypercalciuria or hypervitaminosis D.

Conclusion: A dose of 300,000 IU of vitamin D3 is comparable to 600,000 IU, administered orally, over a single day, for treating rickets in under-five children although there is an unacceptably high risk of hypercalcemia in both groups. None of the regime is effective in normalization of vitamin D status in majority of patients, 3 months after administering the therapeutic dose.

Key Words: Children, Rickets, Treatment, Serum 25(OH)D, Stoss Therapy, Vitamin D3,

Indian infants and adolescents have a high prevalence of hypovitaminosis D and nutritional rickets [1-3]. Treatment includes therapeutic doses of vitamin D and calcium. In USA, Australia, and UK, the recommended dose and duration of vitamin D therapy is variable with either a high dose bolus therapy (Stoss therapy 200,000-600,000 IU of vitamin D as a single oral or parenteral dose or intermittent high doses) or continuous slow supplementation [4-6]. These recommendations are based on expert opinion and experience rather than sound evidence from randomized comparison of doses. Recent guidelines by Endocrine society recommend 50,000 IU weekly for 6 weeks [7]. Traditionally in India, a single dose of 600,000 IU of vitamin D is used for treating nutritional rickets in children [8]; no national recommendations exist. Recent

reports have raised concerns of hypercalcemia following a therapeutic dose of 600,000 IU of vitamin D [9-11].

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Scientific literature to provide evidence for the best therapy at minimum effective dose – that is feasible, economical and free of potential adverse effects – is scarce. The evidence for establishing the minimum effective therapeutic oral dose of vitamin D is limited to only two trials from Turkey [9,12]. These studies concluded equal efficacy of single oral dose of 300,000 IU of vitamin D in comparison to 600,000 IU for treating nutritional rickets in children. However, these studies had small sample size and did not measure vitamin D status. Vitamin D metabolism is influenced by several

factors, including availability of sunlight and sun exposure, skin pigmentation, genetics, and socioeconomic status. Geographical location of Turkey (39.5°N) carries a higher risk for hypovitaminosis D due to inadequate sunshine as compared to India (28°N), sub-Saharan Africa, Latin America and Caribbean which have sufficient sunlight throughout the year [13]. Therefore, the results of these trials may not be applicable to tropical countries in Asia or Africa.

We hypothesized that an oral dose of 300,000 IU of vitamin D3 is not inferior to 600,000 IU for increasing serum 25(OH)D levels and achieving radiological recovery for treatment of vitamin D deficiency rickets of nutritional origin in children between 6 months and 5 years of age, in a tropical setting.

METHODS

This non-inferiority randomized controlled trial was conducted at a tertiary care hospital attached to a medical school at Delhi, India from November 2010 to April 2012. A clearance from the institutional ethical committee and informed consent from parents were obtained.

Participant selection: Children between the ages of 6 months and 5 years presenting to pediatric outpatient or emergency with a combination of clinical evidence of rickets (wide wrists, bow legs, frontal bossing, rachitic rosary etc.) and radiological findings (fraying, splaying, and cupping at the epiphyseal ends of long bones in wrist/knee) consistent with the diagnosis of nutritional rickets [4,8,14] were eligible for inclusion. Critically ill children and those having coexisting fat malabsorption, liver or renal insufficiency and hypercalcemia were excluded. Children with history of having received vitamin D, calcium supplements, or other medications affecting vitamin D metabolism (*e.g.*; anticonvulsants, steroids, cancer chemotherapy) in previous 6 months were also excluded.

Data collection: Baseline assessment included a detailed socio-demographic and clinical history and physical examination at the time of enrolment. Anthropometry (weight, height/length, head circumference) was recorded as per standard techniques [15]. WHO Child Growth Standards were used as reference population [16]. The Z-scores for anthropometric parameters were calculated for each child using the "WHO Anthro software for PC" [17]. X-rays of the wrist and knee were obtained for all participants at enrolment, as per standard procedures [18]. At enrolment, a venous blood sample was obtained for the estimation of serum calcium, serum phosphorus, serum alkaline phosphatase, serum 25(OH)D, serum

parathormone (PTH), serum albumin, serum glutamate amino transaminase (SGPT) and serum creatinine.

Randomization and Intervention: Randomization was done by block randomization (18 blocks of 4 each and 2 blocks of 2 participants each) to 300,000 IU or 600,000 IU of oral vitamin D3 in a single day. Allocation concealment was done by sealed envelope technique. Each dose consisted of vitamin D3 [cholecalciferol D₃ (C₂₇H₄₄O); Mankind Pharma Limited, Delhi, India] in granular form dissolved completely in 30 mL of milk. The doses were given at an interval of 2 hours under direct supervision (SR) and all children were kept in hospital for 48 hours, or 24 hours after the last dose of the study medication; whichever was later. During the stay, participants were monitored for adverse effects, including vomiting, irritability, headache, crying, abdominal distension, rash and hypertension. At discharge, all children were advised to continue calcium supplementation (30-50 mg/kg/d) orally for 12 weeks. At the end of the study (12 weeks), all children were advised oral vitamin D3 supplementation (400-1000 IU daily) for next 3 months.

Follow-up: All children were asked to report for follow-up at 1 week (± 3 d), 4 weeks (± 1 week), and 12 weeks (± 2 weeks) after enrolment. At each visit, an interval history was obtained for adverse effects such as headache, vomiting, abdominal pain, seizures or bulging fontanelle. A urine sample (5 mL) for estimation of urinary calcium to creatinine ratio was collected at 1 and 12 weeks after enrolment. At 4 weeks, a venous blood sample (2 mL) was taken for serum calcium estimation. Serum 25(OH)D and PTH levels were estimated at baseline and 12 weeks; simultaneous samples were also drawn for serum calcium, serum phosphorus and serum alkaline phosphatase. X-rays of the wrist and knee were repeated at 12 weeks. Follow-up was ensured by telephone or by personal visit.

Serum samples for 25(OH)D and PTH were stored at -20° C and analyzed at completion of study. Commercial kits using radioimmunoassay methods by using gamma counter were used for estimation of serum 25(OH)D (DiaSorin Inc, USA; interassay variation: 11%; intra-assay variation: 12.5%) and PTH (Immunotech SAS, France; interassay variation: 10.3%; intra-assay variation: 7.7%). Serum 25(OH)D levels were categorized as deficient: <20 ng/mL and normal: ≥ 20 ng/mL [7]. Hypocalcemia and hypophosphatemia were defined as serum calcium <8.8 mg/dL and serum phosphorus <3.8 mg/dL, respectively [19].

Outcome measures: Serum levels of 25(OH)D, measured 12 weeks after intervention, served as the

primary outcome variable. Secondary outcome variables included radiological healing, improvement in the radiological severity scores, serum parathormone level and proportion of children with normal serum alkaline phosphatase. Serum alkaline phosphatase was measured using Liquick Cor ALP (PZ CORMAY.SA) and normal levels were defined as per age categories (1–12 months: 82–283 U/L, 13–36 months: 104–345 U/L, >37 months: 93–309 U/L). PTH levels between 10–65 pg/mL at 12 weeks following administration of therapeutic dose of vitamin D3 were considered normal. Radiological healing and severity scores were calculated as described by Thacher, *et al.* [20]. Children were categorized as having mild (score ≤ 4), moderate (score 5–8), and severe radiological changes (score > 8).

Adverse effects – clinical (headache, vomiting, abdominal pain, seizures, symptoms of pseudotumor cerebri) and biochemical (hypercalcemia, urine calcium/creatinine ratio, hypervitaminosis D) – were also compared between the two groups. Hypervitaminosis D was defined as level greater than 150 ng/mL [20] and hypercalcemia was defined as serum calcium greater than 10.8 mg/dL [19]. A urine calcium-creatinine ratio of more than 2 was considered as sign of toxicity [21].

Sample size: Our past experience suggested that the serum level of 25(OH)D (primary outcome) follows log-normal distribution. Sample size for this study was thus calculated on the basis of geometric mean (GM) ratio and decided to set non-inferiority lower boundary for mean GM ratio to be 0.8 at 12 weeks. The geometric mean (GM) ratio indicates geometric mean of 25(OH)D in Group 1 divided by GM of 25(OH)D in Group 2. Using the coefficient of variation as 0.31 with one-sided 2.5% level of significance and 80% power, a sample size of 34 subjects in each group was considered adequate. Co-efficient of variation was calculated on results of a previous study by Soliman, *et al.* [22] assuming mean (SD) level of 28.2 (8.7) ng/mL of 25(OH)D after 3 months of receiving 10,000 IU/kg (maximum 150,000 IU) of vitamin D. Adding expected 10% lost to follow-up, 38 children per group were considered appropriate for this non-inferiority trial.

Statistical analysis: The baseline data were presented in mean and standard deviation for continuous variables and in proportions for categorical variables. Natural log transformation was applied for 25(OH)D, serum parathormone, and alkaline phosphatase because of skewed distribution of these parameters; results were presented in geometric mean and their 95% confidence intervals.

Two factor repeated measures analysis of variance

(ANOVA) was applied to compare baseline and 12 weeks levels of serum 25(OH)D, PTH, calcium, phosphorus, and alkaline phosphatase. The interaction between the group and time was tested. Analysis of covariance (ANCOVA) was applied to compare the serum 25(OH)D levels at 12 weeks between the groups taking baseline value as covariate, and data expressed as geometric mean and 95% confidence intervals for log transformed variable; and mean \pm SD for other continuous variables. Homogeneity of slope assumption of analysis of covariance was tested by including the interaction (group \times baseline value). The value of serum 25(OH)D, serum parathormone, and alkaline phosphatase were expressed as relative change due to log transformation and calcium, phosphorus, and alkaline phosphatase were expressed as mean change. The least square means (estimated marginal means) resulting from the ANCOVA was used to calculate the one side 97.5% confidence interval for log transformed difference between the two treatment groups. The acceptable lower limit of one-sided 97.5% confidence interval of serum 25(OH)D level at dose 300,000 IU was set at 80% of that achieved in the group receiving 600,000 IU of vitamin D3. Intention to treat analysis was also used in full-analysis set considering baseline value as carried forward at 12 weeks.

Analysis was done with SPSS-20 (Chicago, IL).

RESULTS

Enrolment and baseline characteristics: A total of 312 children with rickets were diagnosed over 18 months, of which 106 met the inclusion criterion. **Fig. 1** shows the enrolment and follow-up of children assessed in the study. Of the 76 children enrolled, 45 ($n=34$) were females. Baseline demographic, clinical, and biochemical features; and radiological score of children in the two Groups are shown in **Table I**.

The presenting complaints included not gaining height ($n=43$, 56.6%), irritability ($n=30$, 39.5%), delayed gross motor development ($n=29$, 38.2%), bowing of legs ($n=19$, 25%) hypocalcemic convulsions ($n=13$, 17%), bone pains ($n=4$, 5.5%), delayed tooth eruption ($n=1$, 1.3%) and recurrent infections ($n=61$, 80.3%). Recurrent infections included respiratory tract infections ($n=52$) and diarrhea ($n=9$).

On examination, most frequent clinical findings were wrist widening ($n=76$, 100%), frontal bossing ($n=72$, 94.7%), protruded abdomen ($n=64$, 84%), rachitic rosary ($n=62$, 81.6%), Harrison sulcus ($n=60$, 79%), genu varum ($n=46$, 61.8%), genu valgum ($n=1$, 1.3%), wide open anterior fontanel ($n=29$, 38.7%), hypotonia of

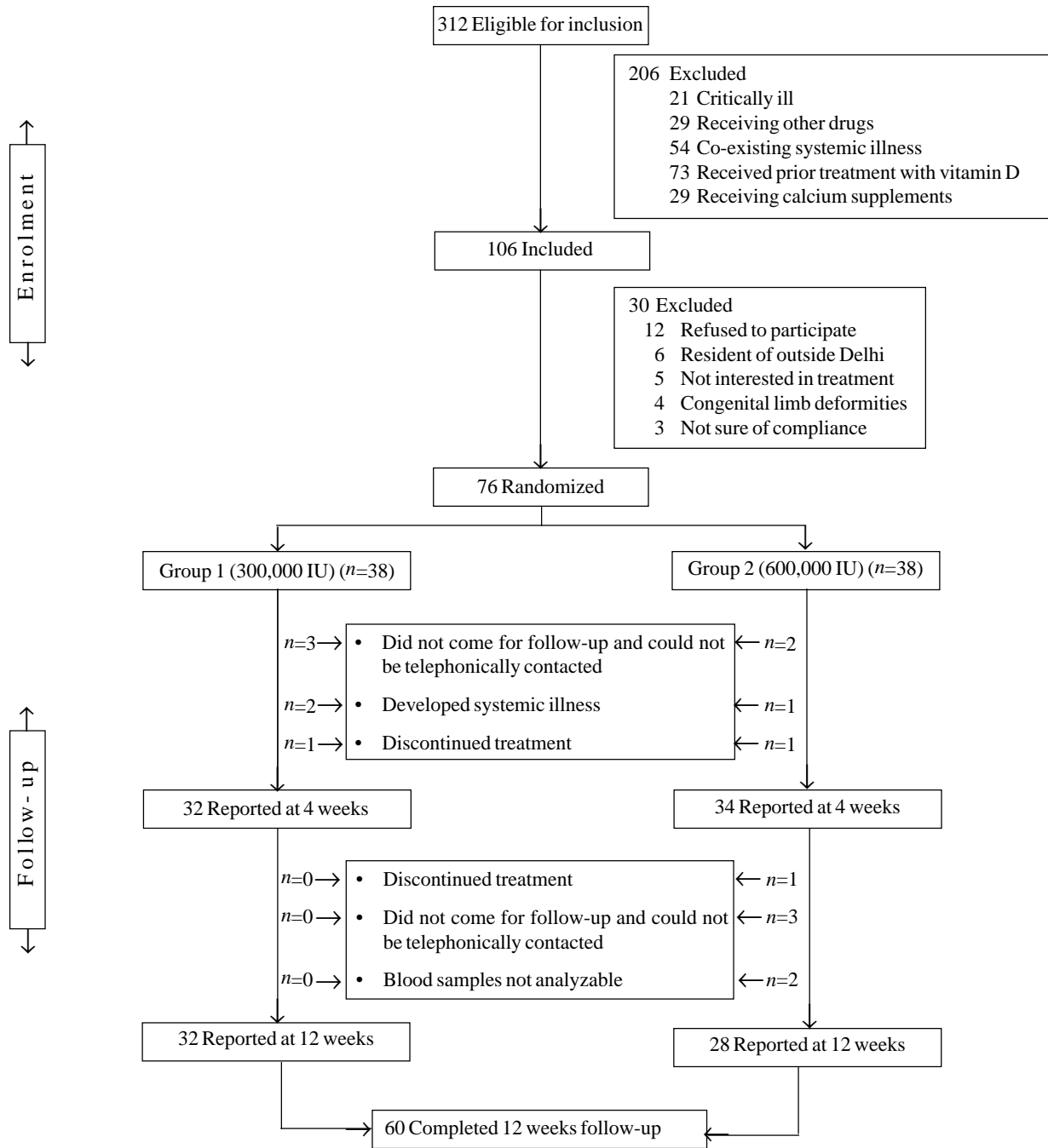


Fig.1 Participant flow diagram.

limbs ($n=4$, 5.5%), delayed tooth eruption ($n=3$, 3.9%) and enamel defects ($n=2$, 2.5%).

Biochemical abnormalities included raised alkaline phosphatase ($n=76$, 100%), hypocalcemia ($n=63$, 82.9%) and hypophosphatemia ($n=47$, 61.8%). The median value (IQR) of serum alkaline phosphatase,

serum phosphorus and serum calcium were 843.50 (582–333.5); 3.2 (2.5–4.3) mg/dL, and 7.8 (6.8–8.5) mg/dL, respectively. Serum parathormone levels were elevated (>65 pg/mL) in 43 (56.6%) children at enrolment. Serum 25(OH)D levels were categorized as normal, and deficient in 8 (10.5%) and 68 (89.5) children, respectively.

TABLE I BASELINE CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF ENROLLED CHILDREN

Parameter	Group 1 300,000 IU (n=38) (Mean±SD)	Group 2 600,000 IU (n=38) (Mean±SD)
Age (months)	15.8 ±13.23	19.1 ±14.40
Weight-for-age (Z score)	-2.8 ±1.82	-2.9 ±1.60
Length-for-age (Z score)	-2.3 ± 1.80	-2.9 ± 2.48
Weight-for-length (Z score)	-0.6 ±1.64	-0.1 ± 1.7
Serum vitamin D (ng/mL)	10.5 ± 9.91	9.5 ± 6.9
Log _e (Serum vitamin D)	1.96 ± 0.92	1.95 ± 0.84
Serum parathormone	166.6±151.86	110.8±112.17
Log _e (Serum PTH)	4.53±1.27	4.05±1.25
Serum ALKPO4(U)	981.5±518.4	1096.9±1035.2
Log _e (Serum ALKPO4)	6.77±0.50	6.74± 0.70
Serum calcium (mg/dL)	7.7±1.29	7.7±1.19
Serum phosphorus (mg/dL)	3.5± 1.29	3.3± 1.31

ALKPO4: alkaline phosphatase; vitamin D: 25(OH)D; PTH: parathormone.

Radiological evidence of rickets included fraying and splaying in all children (n=76, 100%). Osteopenia, cupping and loss of demarcation between metaphysis

and epiphysis were seen in 67% (n=51) of children. Mild, moderate and severe radiological changes were present in 29 (38.1%), 6 (7.9%), and 41 (54%) children, respectively. The distribution was comparable between the two groups (data not shown).

Outcome measures: The changes in biochemical parameters in the two groups after 12 weeks of enrolment are compared in **Table II**. Children in both the groups doubled their baseline serum 25(OH)D level. Serum parathormone and alkaline phosphatase declined by approximately 60%. The adjusted ratio of geometric mean of serum 25(OH)D at 12 weeks between the Groups (taking baseline value as covariate) was 0.91 (95% CI: 0.65-1.29) (**Table III**). This is also diagrammatically depicted in **Fig. 2**. The results were almost similar when intention to treat analysis (ITT) approach was applied with baseline observations carried forward for 25(OH)D.

At 12 weeks, all children in both the groups demonstrated evidence of radiological healing. The mean (SD) radiological severity scores improved significantly (P<0.001) in both the groups after 12 weeks of intervention [Group 1: 2.3 (1.25); Group 2: 2.6 (1.31)]. Improvement in scores was comparable between the groups at 12 weeks. There was no child in either

TABLE II COMPARISON BETWEEN BASELINE AND 12 WEEKS VALUE OF BIOCHEMICAL VARIABLES

Variable	Baseline Geometric mean (95% CI)	12 Weeks [#] Geometric mean (95% CI)	Relative change from baseline: (95% CI)	P-value(interaction between time and Groups)
Serum 25(OH)D (ng/mL)				
G-1	7.58 (5.50-10.44)	16.06 (12.71-20.29)	2.12 (1.42-3.17)	0.42
G-2	6.57 (4.66-9.25)	17.60 (13.71-22.60)	2.68 (1.73-4.13)	
Serum parathormone (pg/mL)				
G-1	80.24 (50.30-127.99)	24.15 (18.19-32.06)	0.30 (0.20-0.46)	0.19
G-2	46.40 (28.73-78.09)	21.59 (16.72-27.88)	0.47 (0.28-0.78)	
Serum alkaline phosphatase (U/L)				
G-1	851.3 (693.0-1045.2)	347.2 (289.8-416.6)	0.41(0.37-0.50)	0.48
G-2	809.2 (654.6-1000.3)	369.8 (306.7-446.3)	0.46 (0.35-0.59)	
Serum calcium (mg/dL)				
G-1	7.54 ± 1.38	9.14 ± 0.68	*1.62 (1.07-2.18)	0.68
G-2	7.64 ± 1.15	9.08 ± 1.03	*1.47(0.98-1.96)	
Serum phosphorous (mg/dL)				
G-1	3.55 ± 1.25	4.59 ± 1.08	*1.04 (0.44-1.64)	0.77
G-2	3.79 ± 3.66	4.65 ± 1.11	*0.86 (-0.30-2.01)	

*Mean change (12 weeks – base line) (95% CI); G-1: Group-1 (Vitamin D 300,000 IU; n=32); G-2: Group-2 (Vitamin D 600,000 IU; n=28). Analysis of variance used for within group and between group differences. All differences are unadjusted; [#]P value <0.001 for within group changes for all variables, except serum phosphorus where P = 0.003.

TABLE III COMPARISON OF BIOCHEMICAL PARAMETERS BETWEEN THE GROUPS, 12 WEEKS AFTER INTERVENTION

Variable	*Estimated marginal geometric means (95% CI)		Relative change[ratio of geometric means (95% CI)]
	Group 1 (n=32) (300,000 IU)	Group 2 (n=28) (600,000 IU)	
Serum 25(OH)D (ng/mL)	16.1 (12.68-20.35)	17.6 (13.67-22.67)	0.91 (0.65-1.29)
Serum parathormone (pg/mL)	23.1 (17.98-29.73)	22.7 (17.34-29.73)	0.98 (0.70-1.47)
Serum alkaline phosphatase (U/L)	345.2 (290.3-407.5)	372.8 (312.0-445.4)	0.92 (0.72-1.19)
Serum calcium (mg/dL)	#9.2 (8.88-9.50)	#9.1 (8.71-9.38)	\$0.14 (-0.311-0.598)
Serum phosphorous (mg/dL)	#4.6 (4.20-4.98)	#4.7 (4.23-5.07)	-\$0.06 (-0.629-0.515)

*Analysis of covariance with baseline value adjusted as covariate; Homogeneity of slope assumption is fulfilled for all the five variables ($P > 0.05$);

Estimated marginal means (95% CI); \$ Mean change (95% CI)

group with radiological severity score >8 ; only one child in Group 1 and 2 children in Group 2 had radiological severity score 5-8; and 31 children in Group 1 and 26 children in Group 2 had severity scores ≤ 4 , respectively.

Almost half the children in both the groups showed normalization of alkaline phosphatase levels after receiving vitamin D3 treatment at 12 weeks [Group 1: 17/32 (53%); Group 2: 15/28 (54%)]. Secondary hyperparathyroidism (serum PTH >65 pg/mL) was present in 65.8% (25/38) children of Group 1 and 47.4% (18/38) children of Group 2 at enrolment. At 12 weeks, only 4 children in Group 1 and one child in Group 2 had raised serum PTH levels. **Web Fig. 1** shows the distribution of children categorized according to serum 25(OH)D levels (both at baseline and 12 weeks after therapy). **Web Fig. 2** shows the increase in serum 25(OH)D in each child in both the groups after 12 weeks of treatment.

Adverse effects: No child required a repeated dose of study medication or developed any signs of drug intolerance (nausea, vomiting, headache, persistent crying, etc.). No clinical adverse effects of Vitamin D3

therapy or infections were noticed in both the groups. During first week, 5 children had diarrhea (Group 1: 2, Group 2: 3). Four children developed respiratory tract infection in second week (Group 1: 2, Group 2: 2).

Laboratory parameters showed no signs of raised urinary calcium creatinine ratio at 1 and 12 weeks. The mean (SD) urinary calcium creatinine ratio in both the groups was comparable [Group 1: 1.2 (1.03), Group 2: 1.2 (0.86); $P = 0.92$]. At 12 weeks also, all children had normal urinary calcium creatinine ratio, and mean (SD) levels were comparable in both the groups [Group 1: 1.0 (0.81), Group 2: 0.9 (0.7); $P = 0.8$].

No child had evidence of hypervitaminosis D. Hypercalcemia was documented in 2 children (1 in each Group) at 4 weeks; and 3 children (1 child in Group 1 and 2 children in Group 2) at 12 weeks.

DISCUSSION

In this study on 76 children (6 mo–5 y) with nutritional rickets, a therapeutic oral dose of 300,000 IU of vitamin D3 was comparable to 600,000 IU for improving 25(OH)D status after 12 weeks of its administration. All children in both the groups demonstrated radiological healing at 12 weeks. Also, there was comparable improvement in radiological severity scores, and comparable decline of serum parathormone and alkaline phosphatase levels in both the treatment arms. We concluded that 300,000 IU of vitamin D3 is not inferior to 600,000 IU for treating nutritional rickets in under-five children. There is a potential risk of hypercalcemia with both regimes.

Our study had certain limitations. The diagnosis of rickets was on clinical and radiological parameters: biochemical indices were not included. Seven (9.2%) children were vitamin D sufficient (serum 25(OH)D >20 ng/mL) but had clinical and radiological evidence of rickets. A previous study by Voloc, *et al.* [7] has

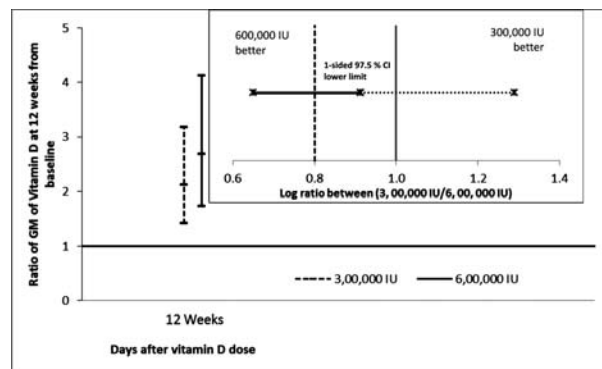


Fig. 2 Ratio of geometric means from baseline to 12 weeks (main graph) and mean ratio between the doses (inset graph).

demonstrated poor correlation between clinical features and serum 25(OH)D levels. Radiological changes in rickets may also be due to hypocalcemia in face of sufficient serum 25(OH)D levels [26]. We did not differentiate between calcium deficient rickets and vitamin D-deficient disease. We also did not study the effect of vitamin D3 therapy on clinical improvement (nutritional status, reversal of deformities). A valid interpretation of our results on adverse effects is also not possible due to limitation of small sample size for adverse effects as an outcome measure. We did not estimate serum 25(OH)D levels at 1 week after therapy, which would have been a better indicator of immediate toxicity.

There was smaller increase in 25(OH)D levels in our study (10.8 ng/mL) as compared to that by Soliman, *et al* (21.95 ng/mL) [22]. Lower increase in mean levels of 25(OH)D may be related to complex mechanisms in pharmacokinetics and pharmacodynamics of vitamin D leading to difference in individual responses, altered vitamin D metabolism in Asian Indians [23], and vitamin D receptor (VDR) polymorphism or mutations [24]. It is also concluded that increase in serum 25OH vitamin D levels are dependent on baseline levels, dose of vitamin D, and weight of patients [25]. Due to a small post-supplementation increase in serum 25(OH)D levels, proportion of children having 25(OH)D level between 5–20 ng/mL remained almost same, before and after treatment.

Our results demonstrate that even a dose of 600,000 IU may not be enough to normalize serum 25(OH)D (beyond 20 ng/mL), in Indian children with rickets. We advised daily vitamin D supplementation for all children for 12 weeks, after completing the study duration of 3 months. We wonder, whether these children should have been started with routine daily vitamin D supplementation, immediately following the mega dose. This approach would have needed a strict monitoring for vitamin D intoxication.

We conclude that a therapeutic oral dose of 300,000 IU of vitamin D can be safely substituted for 600,000 IU for treating nutritional rickets in under-five children. None of the two regimes is effective in normalization of vitamin D status in majority of patients, 3 months after administering the therapeutic dose. Studies are needed to document the optimal strategy of vitamin D3 supplementation in children treated with mega-dose of vitamin D, for replenishing the body stores.

Contributors: The study was conceptualized by PG. Methodology was finalized with inputs from DS, SR, SVM, GM, and RKM. Data were collected by SR and HG. Laboratory support and interpretation was provided by SVM.

GM was responsible for assessment and interpretation of radiological results. The manuscript was drafted by HG and SR with inputs from SVM, GM, and RKM. Statistical analysis was planned and conducted by PG and RKM. PG and DS critically reviewed the manuscript for intellectual content. All authors approved the final paper. PG shall stand as the Guarantor.

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Competing interests: None stated.

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