A Randomized Controlled Trial on Safety and Efficacy of Single Intramuscular versus Staggered Oral Dose of 600 000IU Vitamin D in Treatment of Nutritional Rickets

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Summary

Objective: Comparison of efficacy and safety of two different regimens of vitamin D—600 000IU as a single intramuscular dose, and 60 000IU orally once a week for 10 weeks—in treatment of nutritional rickets.

Methods: Children with nutritional rickets (age: 0.5–5 years, n = 61) were randomized to receive either 60 000IU vitamin D orally once a week for 10 weeks or 600 000IU single intramuscular injection. Serum calcium, phosphate, alkaline phosphatase, urinary calcium/creatinine ratio, serum 25 hydroxy vitamin D and radiological score were compared at 12-week follow-up.

Results: No difference was found in efficacy of the two regimens on comparing biochemical and radiological parameters. Serum 25 hydroxy vitamin D >100 ng/ml was found in two children in the oral group and one child in the intramuscular group. No child developed hypercalcemia or hypercalciuria after starting treatment.

Conclusion: Staggered oral and one-time intramuscular administrations of 600 000IU vitamin D are equally effective and safe in treatment of nutritional rickets.

Key words: Vitamin D, 25(OH)D, radiological score, nutritional rickets.

Introduction

Role of vitamin D and calcium in treatment of nutritional rickets is well established. Most authorities recommend daily or weekly administration of vitamin D orally or parenterally in treatment of rickets [1–3]. A common practice is to administer vitamin D 600 000IU intramuscularly as a bolus dose. Although convenient, administration of a large single dose of vitamin D is reported to cause hypercalcemia and hypercalciuria, thereby raising a concern about its safety [4–6]. Asymptomatic hypercalcemia has been implicated in development of nephrocalcinosis and coronary artery disease [7].

There is no consensus on optimal route of vitamin D administration in treatment of rickets. While efficacy of oral administration has been demonstrated, it may not be an optimal therapy when compliance cannot be ensured [8–11]. Lubani et al found a daily oral vitamin D dose to be less effective as compared with a single bolus intramuscular dose [11]. Stogman et al reported equal efficacy of bolus versus staggered oral regimens in treatment of rickets [12].

The present study was planned to compare efficacy and safety of two different regimens of vitamin D—600 000IU as a single intramuscular dose, and 60 000IU orally once a week for 10 weeks—in treatment of nutritional rickets during a 12-week follow-up.

Methods

Study design

This randomized controlled trial was carried out in the Department of Pediatrics, Lady Hardinge...
Medical College, in association with the Department of Biochemistry, Lady Hardinge Medical College, and the Institute of Nuclear Medicine and Allied Sciences, New Delhi, during November 2009–March 2011. The trial was registered with the Clinical Trials Registry of India (REFCTRI/2010/001427).

Study population
Children in the age-group of 6 months to 5 years attending pediatric outpatient department for any reason and demonstrating clinical (bony deformities, genu varum, genu valgum, limb pains, delayed eruption of teeth, etc.) and radiological signs (a score of >1.5 on a 10-point radiological score) of rickets constituted the subjects for the present study. Children with suspected non-nutritional rickets (history of antiepileptic intake, evidence of liver/renal disease, malabsorption state or familial/metabolic disorders) or those who received vitamin D or calcium in preceding 6 months were excluded. Participation was voluntary and written informed consent was taken from the guardian of each child. The study protocol was approved by the Institutional Ethical Committee.

Sample size
It was decided to include a minimum of 60 children with nutritional rickets. The number was arrived at from the past experience of the number of children with the disease expected to present to the hospital during the proposed study period.

Randomization, blinding and intervention
Recruited subjects were randomized by block randomization (variable block size of 8 and 10) to receive one of the following two treatment protocols:

- Single dose of 600,000 IU of vitamin D₃ intramuscularly: intramuscular (I/M) group
- Oral administration of 60,000 IU of vitamin D₃ per week for 10 weeks: oral group
- Opaque sealed envelopes were used for allocation concealment.

Children in the I/M group were given the intramuscular injection in the hospital. Subjects in the oral group were administered vitamin D under direct observation whenever feasible. The first dose of oral vitamin D₃, 60,000 IU was given at enrolment (Calciorl, Cadila Pharmaceuticals, one sachet = 60,000 IU). At first follow-up after 1 week, second dose of one sachet was administered and one sachet was given for administration of third dose at home after 1 week. At second follow-up at 4 weeks, the fourth dose was given under supervision, and six more sachets were given to complete the course at home. The subjects were followed up over phone to ensure compliance. Children in both groups received oral calcium 50 mg/kg/day (Calcium Sandoz, Novartis Pharmaceuticals) for 12 weeks.

Assessment
All children were followed for 12 weeks. Serum total (tCa) and ionic (Ca²⁺) calcium, phosphate (P), alkaline phosphatase (ALP) and urinary calcium/creatinine ratio (U-Ca/Cr, mg/mg) were measured at baseline and during follow-up at Day 7, 4 weeks and 12 weeks. In the I/M group, serum calcium and U-Ca/Cr were also obtained on Day 3. Serum 25 hydroxy vitamin D [25(OH)D] was measured at baseline and at 12 weeks. Radiographs of left wrist and knee were taken at baseline and during follow-up at 4 and 12 weeks.

Serum tCa was measured by Arsenazo III dye method and Ca²⁺ by ion-selective electrode method using the AVL electrolyte analyzer (Roche). Hypocalcemia was defined as serum tCa < 8.8 mg/dl (Ca²⁺ < 4.48 mg/dl) and hypercalcemia as serum tCa > 11 mg/dl (Ca²⁺ > 5.28 mg/dl) [13]. Serum P was measured using ammonium-phosphomolybdate complex method. Hypophosphatemia was defined as serum P < 3.8 mg/dl. ALP was measured using kinetic assay, normal range 145–420 U/L.

U-Ca/Cr was obtained in spot urine sample. Hypercalciuria was defined as U-Ca/Cr > 0.53 in <1-year age-group, > 0.437 in 1–2-year age-group and > 0.35 in 2–5-year age-group [14].

Serum [25(OH)D] was estimated using 25-hydroxy vitamin D₁₂₅I RIA kits (DiaSorin). For this, 2 ml of serum sample obtained at baseline and at 12 weeks was stored at −20°C until assayed. Vitamin D sufficiency was defined as serum 25(OH)D level 20–100 ng/ml, excess as 100–150 ng/ml and toxicity as >150 ng/ml [1].

Radiographs of left wrist and knee were evaluated using the method developed by Thacher and colleagues and were scored on a 0–10-point scale [15]. A score of >1.5 indicates rickets. This evaluation was done by a separate observer blinded to treatment allocation.

Outcome variables
Safety of therapy was estimated by assessing the proportion of subjects developing hypercalcemia, hypercalciuria and serum 25(OH)D > 100 ng/ml in the two treatment groups at any assessment point. Efficacy of the two regimens was compared by fall in the radiological score and ALP level and normalization of serum Ca, phosphate and serum 25(OH)D concentration.

Statistical analysis
The data were analyzed using Windows SPSS software (version 14). Differences between means were compared by t test and proportions by Z test. Regression analysis and Pearson coefficient were used to find correlation between two variables.
Results

Of 76 cases of rickets evaluated for recruitment, five were excluded. Remaining 71 cases were randomized to receive the two treatment regimens (Fig. 1).

Baseline characteristics

Only 32.8% cases presented with complaints primarily due to rickets. These included hypocalcemic seizures, bowlegs and delayed walking. In the remaining, rickets was detected as an incidental finding, the presenting illnesses being upper and lower respiratory tract infections and gastroenteritis. These two groups of children did not differ in terms of radiological score or ALP level. There was no difference between the two treatment groups on comparing baseline parameters (Table 1).

Efficacy of the two treatment regimens

In both groups, fall in serum ALP was evident by Day 7, but reached statistical significance by 4 weeks as compared with baseline and continued to fall between 4 weeks and 12 weeks. Rise in serum tCa and P was significant at Day 7 compared with baseline and continued to show a significant rise between Day 7 and 4 weeks in both treatment groups. Whereas tCa level continued to rise in between 4 weeks and 12 weeks in both the treatment groups, P level reached a plateau in the oral group at 4 weeks but continued to rise in the I/M group. Serum Ca\(^{2+}\) level showed a significant increase at Day 7 compared with baseline in the oral group but did not increase significantly between Day 7 and 4 weeks. In the I/M group, Ca\(^{2+}\) did not rise significantly at Day 7 but increased between Day 7 and 4 weeks and then reached a plateau at 4 weeks (Table 2).

Total cases of rickets screened: 76

<table>
<thead>
<tr>
<th>Excluded: 5 cases included in study: 71</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/M group: 37</td>
</tr>
<tr>
<td>Lost: 6</td>
</tr>
<tr>
<td>completed 12 weeks</td>
</tr>
<tr>
<td>Follow up: 31</td>
</tr>
</tbody>
</table>

Fig. 1. Study flowchart.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Treatment groups</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral group (n = 34)</td>
<td>I/M group (n = 37)</td>
</tr>
<tr>
<td>Age (months)</td>
<td>12.81 ± 7.14</td>
<td>13.33 ± 7.92</td>
</tr>
<tr>
<td>Weight for age Z-score</td>
<td>−0.46 ± 0.96</td>
<td>−0.52 ± 0.91</td>
</tr>
<tr>
<td>Height for age Z-score</td>
<td>−1.09 ± 0.88</td>
<td>−1.06 ± 0.86</td>
</tr>
<tr>
<td>Serum total calcium (mg/dl)</td>
<td>8.78 ± 1.07</td>
<td>8.75 ± 1.06</td>
</tr>
<tr>
<td>Serum ionic calcium (mg/dl)</td>
<td>4.22 ± 0.65</td>
<td>4.39 ± 0.46</td>
</tr>
<tr>
<td>Serum phosphate (mg/dl)</td>
<td>2.89 ± 0.97</td>
<td>2.99 ± 0.94</td>
</tr>
<tr>
<td>Serum ALP (IU/L)</td>
<td>823.13 ± 373.07</td>
<td>946.77 ± 486.50</td>
</tr>
<tr>
<td>Serum 25(OH)D (ng/ml)</td>
<td>6.51 ± 10.79</td>
<td>6.50 ± 7.53</td>
</tr>
<tr>
<td>Radiological score</td>
<td>7.11 ± 2.07</td>
<td>8.04 ± 2.20</td>
</tr>
</tbody>
</table>
### TABLE 2

<table>
<thead>
<tr>
<th>Assessment point</th>
<th>S. ALP (IU/L)</th>
<th>p value (oral vs. I/M)</th>
<th>S. total calcium (mg/dl)</th>
<th>p value (oral vs. I/M)</th>
<th>S. phosphorus (mg/dl)</th>
<th>p value (oral vs. I/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>823.13 ± 373.07</td>
<td>0.27</td>
<td>8.78 ± 1.07</td>
<td>0.90</td>
<td>4.22 ± 0.66</td>
<td>0.34</td>
</tr>
<tr>
<td>Day 7</td>
<td>810.06 ± 534.26</td>
<td>0.27</td>
<td>8.65 ± 0.84</td>
<td>0.27</td>
<td>4.40 ± 0.28</td>
<td>0.21</td>
</tr>
<tr>
<td>4 weeks</td>
<td>378.90 ± 334.43</td>
<td>0.27</td>
<td>10.06 ± 0.54</td>
<td>0.66</td>
<td>4.55 ± 0.34</td>
<td>0.21</td>
</tr>
<tr>
<td>12 weeks</td>
<td>204.60 ± 101.70</td>
<td>0.96</td>
<td>10.46 ± 0.16</td>
<td>0.76</td>
<td>4.77 ± 0.13</td>
<td>0.44</td>
</tr>
</tbody>
</table>

*Intragroup comparison at various assessment points (only significant values are reported):*  
Serum ALP; p value: Day 7 vs. baseline <0.001 in both the groups.  
Serum ALP; p value: Day 7 vs. baseline <0.001 in both the groups.  
Serum phosphorus; p value: oral group <0.001 vs. I/M group at 4 weeks <0.001 in both groups.

There was no significant difference in mean serum ALP, tCa and P levels at baseline or at 7-day, 4-week and 12-week follow-up in the two groups. Mean serum Ca$^{2+}$ was lower in the oral group compared with the I/M group at 4 weeks but not at Day 7 or 12 weeks. There was no significant difference between the groups on comparing proportion of children with biochemical features suggestive of rickets at any point of the study ($p > 0.05$), except that at the 4-week follow-up, there were more cases of hypocalcemia in the oral group ($p = 0.039$) (Table 3).

There was a significant fall in the mean radiological score after 4 and 12 weeks in both groups. The mean radiological scores of the two treatment groups did not differ significantly at baseline or during follow-up. Proportionate fall in the radiological score was higher in the I/M group compared with the oral group at 4 weeks ($p < 0.001$) but not at 12 weeks ($p = 0.62$). All children had a radiological score $>1.5$ before starting treatment, but at 12 weeks, only one child from each group had a radiological score $>1.5$ (Table 4).

There was no difference in mean serum 25(OH)D in the two groups at baseline (oral group: 6.51 ± 10.79 ng/ml, I/M group: 6.50 ± 7.53 ng/ml, $p = 0.998$) and 12 weeks (oral: 38.09 ± 28.44 ng/ml, I/M: 39.63 ± 26.19 ng/ml, $p = 0.887$). The increase in serum 25(OH)D in both the groups was statistically significant ($p < 0.001$ in both) at 12 weeks as compared with baseline. Twenty-nine of 30 (96.67%) children in the oral group and 29 of 31 (93.55%) children in the I/M group had serum 25(OH)D level $<20$ ng/ml before initiation of therapy. After 12 weeks, nine children in each treatment group (30% in the oral group, 29.03% in the I/M group) still had serum 25(OH)D level $<20$ ng/ml. The proportion of subjects with low serum 25(OH)D level at the end of study period did not differ between the groups ($p = 0.467$) (Fig. 2).

On comparing children with post-treatment serum 25(OH)D levels $<20$ ng/ml with those who had $25$ (OH)D level $>20$ ng/ml, no difference was observed in change in radiological score, or in mean serum ALP, calcium and phosphate levels.

Safety of the two treatment regimens  
Mean U-Ca/Cr was 0.37 ± 0.35 in the oral group and 0.4 ± 0.44 in the I/M group at baseline. There was no significant change in the ratio at Day 7, 4 weeks or 12 weeks. The mean ratios in the two treatment groups did not differ significantly at any evaluation point. Four children from the oral group and five from the I/M group had elevated U-Ca/Cr at baseline, but these ratios did not increase further with the treatment. No child developed hypercalciuria after starting of treatment during the study period.

No patient was hypercalcemic at treatment initiation. Four weeks after treatment, two children in
TABLE 3

Number (%) of children with biochemical parameters suggestive of rickets in the two treatment groups

<table>
<thead>
<tr>
<th>Assessment points</th>
<th>% Children with hypocalcemia (ionic calcium &lt; 4.48 mg/dl)</th>
<th>p-value</th>
<th>% Children with hypophosphatemia (serum phosphate &lt; 3.8 mg/dl)</th>
<th>p-value</th>
<th>% Children with elevated ALP (&gt; 420 IU/L)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral group (n = 30) vs. I/M group (n = 31)</td>
<td></td>
<td>Oral group (n = 30) vs. I/M group (n = 31)</td>
<td></td>
<td>Oral group (n = 30) vs. I/M group (n = 31)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>13 (43.33%) vs. 11 (35.48%)</td>
<td>0.27</td>
<td>25 (83.33%) vs. 23 (74.19%)</td>
<td>0.19</td>
<td>25 (83.33%) vs. 28 (90.32%)</td>
<td>0.21</td>
</tr>
<tr>
<td>At 7 days</td>
<td>6 (20%) vs. 9 (29.03%)</td>
<td>0.21</td>
<td>17 (56.67%) vs. 15 (48.39%)</td>
<td>0.26</td>
<td>24 (78.00%) vs. 27 (87.09%)</td>
<td>0.23</td>
</tr>
<tr>
<td>At 4 weeks</td>
<td>5 (16.67%) vs. 1 (3.33%)</td>
<td><strong>0.04</strong></td>
<td>7 (23.33%) vs. 7 (22.58%)</td>
<td>0.47</td>
<td>10 (33.33%) vs. 8 (25.80%)</td>
<td>0.26</td>
</tr>
<tr>
<td>At 12 weeks</td>
<td>0% vs. 0%</td>
<td></td>
<td>1 (3.3%) vs. 0%</td>
<td>0.15</td>
<td>1 (3.33%) vs. 2 (6.45%)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Figures in bold indicate statistical significance.

TABLE 4

Comparison of radiological score between the two treatment groups

<table>
<thead>
<tr>
<th>Assessment points</th>
<th>Mean radiological score (oral vs. I/M)</th>
<th>p-value</th>
<th>% of children with radiological score &gt; 1.5 (oral vs. I/M)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oral group (n = 30) vs. I/M group (n = 31)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.12 ± 2.07 vs. 8.04 ± 2.21</td>
<td>0.95</td>
<td>30 (100%) vs. 31 (100%)</td>
</tr>
<tr>
<td>4 weeks</td>
<td>4.36 ± 1.766 vs. 3.61 ± 1.40</td>
<td>0.69</td>
<td>29 (96.67%) vs. 29 (93.55%)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>0.58 ± 0.63 vs. 0.56 ± 0.54</td>
<td>0.90</td>
<td>1 (3.3%) vs. 1 (3.23%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Intragroup comparison: p values for mean radiological score: 4 weeks vs. baseline <0.001 and 12 weeks vs. 4 weeks <0.001 in both the groups.

Fig. 2. Distribution of subjects according to their serum vitamin D status (n = 71).
the oral group and three in the I/M group had elevated tCa levels (range: 11.2–12.1 mg/dl). At the end of treatment, two children in each group had elevated tCa levels. None of these children had elevated serum 25(OH)D levels or developed hypercalciuria at any point of time. Further, serum Ca$^{2+}$ levels remained within the normal limit (<5.28 mg/dl) in all children.

Excess vitamin D was found in 2 of 30 children in the oral group (105.4 ng/ml, 103.6 ng/ml) and 1 of 31 children in the I/M group (106.10 ng/ml) at 12 weeks ($p = 0.267$). Two children among these had hypercalciuria, but this was present even at the baseline when serum 25(OH)D level was low, and their U-Ca/Cr did not increase with treatment.

**Discussion**

We have shown that a 600 000IU dose of vitamin D administered through the oral or intramuscular route is effective in treatment of nutritional rickets. Twelve weeks after therapy, serum calcium normalized in all cases. Serum phosphate normalized in 97% cases in the oral group and in all cases in the I/M group. Serum ALP level started to fall significantly after 4 weeks of therapy and continued to fall until the end of therapy in both the treatment groups. All children had radiological score $>1.5$ at the initiation of therapy, but at the end of treatment, all but one child in each group had score $\leq 1.5$, indicating complete healing. Combined end point of ALP <420 IU/L and radiological score $\leq 1.5$ was achieved in 28 of 30 (93.33%) subjects in the oral group and 28 of 31 (90.32%) subjects in the I/M group, indicating equal efficacy of both routes of administration.

Healing started slower in the oral as compared with the I/M group. Mean serum ionic calcium was lower, and proportion of children with hypocalemia was higher in the oral as compared with the I/M group at 4 weeks. Also, proportionate fall in the radiological score was significantly higher in the I/M compared with the oral group at 4 weeks. However, this difference was not apparent at subsequent follow-up. It has previously been reported that oral administration of bolus dose of vitamin D causes a prompt increase in serum 25(OH)D level compared with intramuscular administration, which causes slower and delayed increase [16, 17]. It is likely that staggered rather than one-time administration of oral vitamin D in our study caused healing to proceed slowly in the initial weeks, with subsequent catch-up.

Lubani et al [11] have reported lower efficacy of oral daily vitamin D administration in treating rickets compared with single large intramuscular administration. Authors conceded that failure of oral regimen may be due to lack of compliance. Using a comparatively lower oral dose as compared with an intramuscular dose may be another factor for failure of the oral regimen in that study. One of the factors contributing to good efficacy of oral regimen in our study would be strict measures taken to ensure compliance with therapy.

After completion of therapy, there were nine patients in each group (total 18/61, 29.50%) who had serum 25(OH)D <20 ng/ml. Biochemical and radiological parameters of healing in these children were similar to those with serum 25(OH)D >20 ng/ml after completion of therapy, indicating that healing commenced at equal pace in both groups, despite lower increment in serum vitamin D in the former group. It is likely that co-administration of calcium in our study contributed toward healing. In South Africa and Nigeria, calcium alone (350–1000 mg per day) was found to be effective in healing of nutritional rickets, and to be more efficacious than vitamin D therapy alone [18, 19]. Besides, in our previous studies, we found low calcium intake in patients with rickets, and the subjects receiving both calcium and vitamin D demonstrated better healing that those receiving vitamin D alone [20, 21]. Thus, calcium supplements were continued through this study period, despite normalization of serum calcium in most subjects by 4 weeks. However, in subjects with rickets assessed to have an adequate calcium intake, one may consider discontinuing calcium supplements once calcium levels normalize.

Concerns have been raised about safety of administration of 600 000IU of vitamin D, which may lead to markedly elevated serum 25(OH)D levels causing hypercalcemia, hypercalciuria, and nephrocalcinosis [4–6]. The concern regarding safety primarily arose in the previous decades when this dose was used as prophylaxis against nutritional rickets [22, 23]. In our study, mild elevation in serum 25(OH)D level was found in 2 of 30 children in the oral group and 1 of 31 children in the I/M group. None of these children had hypercalciuria at any point of the study. Two of these three children had hypercalcemia, but their baseline U-Ca/Cr was also elevated. Their U-Ca/Cr did not show further increase after treatment with vitamin D.

Some authors have reported hypercalcemia after administration of 600 000IU of vitamin D in treatment of nutritional rickets [4, 5]. In our work, two children in the oral group and three in the I/M group had elevated tCa levels, although their Ca$^{2+}$ levels were within the normal range. All these subjects were clinically asymptomatic throughout the study and did not have either excess 25(OH)D or hypercalciuria. Thus, clinical significance of this mild elevation in 25(OH)D and tCa level, both asymptomatic, is doubtful. However, it would be worthwhile to look at the efficacy of lower doses of vitamin D in treatment of rickets and to assess whether healing can be achieved without associated derangements noted by us. Successful treatment of nutritional rickets using lower doses of vitamin D has been reported by others [8, 24].
A surprising finding was hypercalciuria in nine cases even at baseline, when kidneys are expected to be avidly conserving calcium. Ultrasonography done before treatment commencement did not reveal nephrocalcinosis in these cases. However, spot U-Ca/Cr is not a very sensitive indicator of total daily calcium excretion. Wide fluctuations in the same individual from normocalciuric to hypercalciuric range on different occasions have been reported [25]. In 2006, using data from 14 published studies, suitable spot U-Ca/Cr cutoffs (95th percentile) from birth to 18 years were determined [14]. Our cutoffs were based on this study. We found that children with initial hypercalciuria continued to have elevated urinary calcium/creatinine ratio throughout the study period, but none of these children were hypercalcemic at any point of the study and their calcium/creatinine ratio did not increase after therapy. No child other than these nine developed hypercalciuria during the study. Oduwole et al. recently reported high incidence of incomplete distal renal tubular acidosis and hypercalciuria in children with nutritional rickets [26]. Although not explored by us, incomplete distal renal tubular acidosis may be a possible explanation for baseline hypercalciuria in our subjects.

Although a prospective work with a robust design, our work has several limitations. The number of study subjects was small. As adverse events like hypercalcemia, hypervitaminosis D and hypercalciuria are infrequent, a larger sample size would be more appropriate in determining their incidence. A follow-up beyond 12 weeks would better indicate course of hypercalcemia observed in some cases.

To conclude, results of our study indicate that a dose of 600 000IU vitamin D administered through the oral or the intramuscular route is effective and safe in treatment of nutritional rickets. Occurrence of mild elevation in serum 25(OH)D and total serum calcium levels warrants looking at efficacy of lower doses of vitamin D in treating rickets.

References


