Can Stoss Therapy Be Used in Children with Vitamin D Deficiency or Insufficiency without Rickets?

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Short Running Title: **Vitamin D deficiency and stoss therapy**

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Abstract

Objective: Stoss treatment has also been suggested due to non-skeletal benefits of vitamin D in adults, but no sufficient data are present about the optimal dose of vitamin D replacement in children with vitamin D deficiency/insufficiency without rickets. This study aimed to compare efficiency/side effects of two different stoss therapy regimens (10.000 IU/kg and 300.000 IU vitamin-D_3) administered in children with vitamin D deficiency/insufficiency without rickets.
Methods: Sixty-four children who had vitamin-D deficiency/insufficiency were studied. A serum level of 25-hydroxyvitamin-D(25-OH-D) 15-20 ng/mL was considered vitamin-D insufficient and <15 ng/mL was considered vitamin-D deficient. Children were divided into two groups according to stoss therapy doses. Serum calcium, phosphate, alkaline phosphatase, 25-OH-D, parathyroid hormone, and spot urine calcium/creatinine ratios before/after treatment were recorded. Wrist radiography and renal ultrasonography were performed.
Results: The mean age was 10.6±4.4 years. Thirty-two children were treated with a single vitamin-D3 dose of 10.000 IU/kg and 32 patients received 300.000 IU. No difference was found in 25-OH-D levels between the two groups at presentation. The mean level of 25-OH-D was higher in the 10.000 IU/kg group at the second week of therapy. There was no difference between the groups at post-treatment weeks 4 and 12. The 25-OH-D was found below optimal levels(≥30 ng/mL) in 66.5% and <20 ng/mL in 21.8% of patients at the third month in both groups. None developed hypercalcemia and/or hypercalciuria. Nephrolithiasis was not detected in any patients.
Conclusion: This study showed that both doses of stoss therapy used in the treatment of vitamin D insufficiency/deficiency are effective and safe. However, an optimal level of 25-OH-D cannot be maintained for more than three months.

Keywords: Vitamin D deficiency, rickets, stoss therapy

Introduction

Vitamin D is essential for mineralization of bone, calcium and phosphate homeostasis and neuromuscular conduction (1). Low vitamin D levels lead not only to rickets in children and osteomalasia in adults but also to muscle weakness and predisposition to respiratory infections, hyperparathyroidism, the inability of acquisition of peak bone mass and increased risk of fracture (2). Many clinicians now measure vitamin D levels as part of routine laboratory work and recommend vitamin D supplements often at high doses to their patients for the possible prevention of cancer, cardiovascular disease, diabetes, autoimmune disorders and other conditions because observational studies support that there is a relationship between low vitamin D levels and an increased risk for these situations (3). Stoss treatment has also been suggested due to non-skeletal benefits of vitamin D in adults, but no sufficient data are present for children. However, an optimal treatment dose of vitamin D is not well known in patients with vitamin D deficiency or insufficiency without marked signs of rickets. Despite the efforts of vitamin D supplementation as a public health campaign in the world, a considerable number of children are still at high risk because of the poor adherence of the parents to supplementation regimens. Because

the signs and symptoms of vitamin D deficiency without rickets are insidious or nonspecific, it often goes unrecognized and untreated (4).

In this retrospective study, efficacy and side effects of two different doses of stoss therapy (10.000 IU/kg and 300.000 IU, oral, single dose vitamin D3) in vitamin D deficient or insufficient children without marked signs of rickets were compared.

Methods

The children and adolescents who had been referred to the pediatric endocrinology department due to vitamin D deficiency or insufficiency between January 2014 and January 2015 and treated with two different stoss therapy doses (10.000 IU/kg and 300.000 IU, oral, single dose vitamin $D_{3)}$ were retrospectively studied (5). Patients with chronic diseases such as malabsorption, liver disease, renal disease, gastrointestinal, hematologic and rheumatologic diseases etc., and drug usage influencing vitamin D metabolism were excluded from the study. Patients' age, gender, anthropometric measurements, season of admission and complaints at presentation were recorded. A serum level of 25- hydroxyvitamin D (25-OH-D) between 15-20 ng/mL was considered as vitamin D insufficiency, <15 ng/mL as vitamin D deficiency and <5 ng/mL as severe vitamin D deficiency. The serum levels of calcium, phosphate, alkaline phosphatase (ALP), 25-OH-D, parathyroid hormone, spot urine calcium/creatinine (UCa/UCr) ratio before and after treatment (weeks 2, 4 and 12) and renal ultrasonography (USG) outcomes were compared. Clinical complaints that brought patients to the clinics were recorded and information about whether these complaints continued two weeks after vitamin D therapy were obtained from the patients' records. Laboratory reference values based on age groups were used for defining hypocalcemia, hypophosphatemia, elevated ALP and hyperparathyroidism. UCa/UCr > 0.2 in spot urine was considered as hypercalciuria. Serum Ca, P, and ALP levels were measured with the calorimetric method. Serum PTH and 25-OH-D levels were measured with electrochemiluminescense enzyme immunoassay method (ADVIA Centaur, USADPC Co., USA).

Statistical analysis

Statistical analysis was performed using SPPS 21.0 (SPSS Inc., Chicago, IL, USA) software. All data were given as mean ± standard deviation score (SDS). Homogeneity of the data was assessed using the Kolmogorov-Smirnov test. Differences in the mean level of Vitamin D between the two treatment groups (10.000 IU/kg and 300.000 IU) and between patients with or without symptoms were tested using the student T test for data with normal distribution and the Mann-Whitney U test for data without normal distribution. The Chi-square test was used to compare the frequency of the patients with complaints before and after treatment. The results were expressed with a 95% confidence interval and a p value less than 0.05 was considered statistically significant.

Results

Sixty four patients with the mean age of 10.6 ± 4.4 years were included in the study. Age, gender, anthropometric measurements, season of admission and laboratory data of the patients are shown in Table 1. Of the patients, 32 were treated with 10.000 IU/kg (max 600.000 IU) and the remaining 32 patients received 300.000 IU single dose oral vitamin D3. Severe vitamin D deficiency was determined in 13, vitamin D deficiency in 42 and vitamin D insufficiency in 9 patients. Calcium and phosphate levels were in normal ranges in all patients, while the level of ALP was high in 12, PTH was high in 8 patients. The mean 25-OH-D levels of the groups (10.000 IU/kg and 300.000 IU) were not significantly different before treatment (10.8±4.9 and 8.8±3.6 ng/mL, respectively, p>0.05). Of the patients, 26.6% (n=17) were asymptomatic (n=17). The most common symptoms at presentation were weakness (40.6%), lower back pain, (40.6%), hair loss (37.5%), numbness in hands and feet (28.1%), constipation (20.3%), excessive sweating (15.6%) and frequent respiratory tract infection (12.5%). None of the patients had a history of a clinically significant fracture. More than one complaint was observed in 56% of the patients. When the patients were re-evaluated two weeks after treatment, the number of patients with symptoms were found to be significantly reduced (p<0.05) (Figure 1). The mean level of 25-OH-D was significantly higher in the 10.000 IU/kg group at the second week after treatment (76.6±30.6 vs. 57.4±18.1 ng/mL, p<0.05), but there were no statistically significant differences between the groups in the levels of vitamin D at the 4^{th} and 12^{th} week after treatment (p>0.05) (Figure 2). The level of 25-OH-D was reduced below optimal levels (≥30 ng/mL) in 66.5% and below 20 ng/mL in 21.8% of the patients at 12 weeks post-treatment. None of the patients in both groups developed hypercalcemia, hypercalciuria or vitamin D intoxication. Nephrolithiasis was not detected in any of the patients at the third month of the treatment.

Discussion

The blood level of 25-OH-D, which is defined as vitamin D deficiency remains somewhat controversial. As determined by the measurement of serum concentrations of calcidiol (25-OH-D), vitamin D deficiency is present when values are below 15 ng/mL. Calcidiol concentrations between 15 and 20 ng/mL indicate vitamin D "insufficiency," whereas those >20 ng/mL are adequate or "sufficient" for children (6,7). However, these guidelines, based on the recommendations of the Institute of Medicine report, are not accepted by all authorities and remain the subject of ongoing investigation. Alternate guidelines state that a normal 25-OH-D concentration be defined as greater than 30 ng/mL with values of 20 to 30 ng/mL used to define "insufficiency" and values of

less than 20 ng/mL considered to identify vitamin D "deficiency" especially for adults (8). Vitamin D deficiency in the infant may be managed by administration of vitamin D 1000 to 5000 IU/day. For the child who is one year of age or older, or an adolescent, vitamin-deficient rickets may be treated with 5000 to 10000 IU/day of vitamin D (9). Alternative therapeutic regimens for treatment of rickets include 50,000 IU orally weekly for 8 weeks, the administration of a single oral (or intramuscular) dose of 150,000 to 600,000 units or 10.000 IU/kg of vitamin D_3 (5,10). Our clinical experience has shown us that there is poor patient compliance to long-term low dose vitamin D applications, which may be insufficient to achieve the desired level of vitamin D. We use a 25-OH-D level below 20 ng/mL as a threshold value for pharmacological treatment in our clinic. We prefer stoss therapy rather than long-term low dose vitamin D administration because of poor patient compliance. Indeed, in a previous study, half of 42 infants and children aged between 5 months and 3 years with a 25-OH-D level of <20 ng/mL had been treated with stoss therapy (150.000 IU, single dose, oral) and the remaining were given low dose long term vitamin D_3 therapy (2000 IU/day for 6 weeks) and a better vitamin D level was provided in a stoss therapy group without any side effects observed (11).

The clinical signs of vitamin D deficiency and insufficiency can be variable; asymptomatic, nonspecific clinical findings or obvious rickets signs (4). Studies have shown that the risk of fracture is increased in children with low levels of vitamin D and that they are also sensitive to respiratory tract infections (12,13). In the present study, none of the patients had a history of clinically significant fracture. According to the parents' self reports 12.5% of the patients had experienced frequent respiratory tract infections. Additionally, there were some nonspecific clinical symptoms in a majority of the patients that could not be explained by any illness at admission, which later showed a decrease after vitamin D treatment (Figure 2). However, no relationship was found between these symptoms and the levels of vitamin D. A previous study by Voloc, et al. has reported poor correlation between clinical features and serum 25-OH-D levels (14).

All available evidence suggests that children and adults should maintain a blood level of 25-OH-D above 20 ng/mL to prevent rickets and osteomalacia. However, to maximize vitamin D's effects on calcium, bone, and muscle metabolism, it has been reported that the 25-OH-D blood level should be above 30 ng/mL. Numerous epidemiological studies suggest that a 25-OH-D serum level above 30 ng/mL may have additional health benefits in reducing the risk of common cancers, autoimmune diseases, type 2 diabetes, cardiovascular disease, and infectious diseases (8,15). In the present study, both treatment protocols were effective in providing a sufficient level of Vitamin D, which remained higher in the 10.000 IU/kg treatment protocol group compared to the other protocol at the second week. However, the levels of vitamin D were decreased below the optimal level (≥30 ng/mL) at week 12 of the treatment in a majority of the patients in both groups. Similar to our findings, in a randomized controlled study half of the patients with rickets (mean age 12 months) received 300.000 IU (Group 1) and the other half of patients received 600.000 IU (Group 2) oral vitamin D_3 therapy. The levels of 25-OH-D studied 12 weeks after initiation of the treatment were found to be below 20 ng/ mL in 62.5% of the patients in Group 1 and 64.3% of the patients in Group 2. In that study, the authors reported that both regimens failed to optimize the level of Vitamin D for more than 3 months and no side effects were observed with both regimens (16). Although studies on this topic are limited, both our results and data by Mittal H. et al. suggest that stoss therapy protocols should be repeated once every three months, especially in patients at risk for vitamin D deficiency with a poor compliance to vitamin D supplementation.

There is a lack of consensus on the dose of vitamin D_3 in stoss therapy because of conflicting results from numerous studies. Stoss therapy can lead to side effects such as hypercalcemia, hypercalciuria, and nephrocalcinosis if vitamin D deficiency is not documented before therapy. Studies that compared low- and high-dose stoss therapy in nutritional rickets showed that 150,000 and 300,000 IU of vitamin D were adequate as treatment, but 600,000 IU of vitamin D had a risk of hypercalcemia (17,18). However, there are also studies reporting the use of a dose of 600.000 IU in the treatment of rickets due to vitamin D deficiency without any side effects (19,20). Lubani et al. showed that intramuscular vitamin D at a dose of 600,000 IU was safe and effective. A single dose (600,000 IU) of vitamin D was given to 42 vitamin D-deficient children (aged between 5 and 19 months) by Shah and Finberg; biochemical improvement was detected in 4-7 days and radiological improvement was detected in 10-14 days. Side effects, such as hypercalcemia or hypercalciuria, were not observed. In a recent meta-analysis, no risk was found for hypercalcemia or hypercalciuria in stoss therapy at a single oral dose below 400.000 IU, whereas doses above 400.000 IU created a risk for hypercalcemia (5). In the present study, none of the patients in both groups developed hypercalcemia, hypercalciuria, vitamin D intoxication, or nephrolithiasis.

There are some limitations of this study that need to be acknowledged. Because of its retrospective design, we do not know about the calcium and vitamin D content of patients diets and we have no evidence regarding the cause and effect relationship between the clinical symptoms and vitamin D deficiency at admission.

Unlike other studies in literature, this study has been performed in subjects who had no obvious clinical or radiological signs of rickets. This study shows that stoss therapy could be used in these groups of patients safely without any serious side effects.

In conclusion; this study demonstrated that the two stoss therapy protocols with 10.000 IU/kg and 300.000 IU doses used in the cases of vitamin D insufficiency or deficiency without marked signs of rickets seem not to be superior to each other in terms of efficacy and side effects, but a optimal serum level of 25-OH-D cannot be maintained for more than three months and the treatment dose should be repeated at the 12th week. We believe that these stoss therapy protocols can be used safely, especially in cases with poor patient compliance to vitamin D supplementation in which the optimal level of vitamin D cannot be achieved through nutritional approaches and the encouragement of sunbathing.

Conflicting of Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Table 1: Clinical and laboratory characteristics (before and two weeks after treatment) of patients

Patients	10.000 IU/kg		300.000 IU		p
Age (years)(mean, range)	8.7±4.3 SDS, (3-17)		9.4±3.8 SDS, (3-17)		>0.05
Female /male	19/13		22/10		>0.05
Weight SDS Weight range (kg)	0.06±0.9 13-72		0.12±0.9 16-76		>0.05
Height SDS	-0.21±0.84		0.18±1.0		>0.05
Body mass index (kg/m^2)	0.29±1.1 SDS		0.40±0.8 SDS		>0.05
Admission Spring Summer Autumn Winter	 10% 6% 8% 76%		 12% 4% 4% 80%		>0.05
Calcium (mg/dL)	Before treatment	9.6±0.6	Before treatment	9.5±0.3	>0.05
	After treatment	10.0±0.3	After treatment	9.7±0.4	>0.05
Phosphorus (mg/dL)	Before treatment	4.7±0.6	Before treatment	4.4±0.6	>0.05
	After treatment	4.8±0.6	After treatment	4.5±0.5	>0.05
ALP (IU/L)	Before treatment	260±125	Before treatment	223±158	>0.05
	After treatment	235±93	After treatment	214±150	>0.05
PTH (pg/mL)	Before treatment	56±40	Before treatment	50.1±28.6	>0.05
	After treatment	34.2±12	After treatment	34.5±22	>0.05

Data are given as mean ± SDS (Standart Deviation Score).
ALP: alkaline phosphatase, PTH: parathyroid hormone

Figure 1: The number of patients with symptoms before and two weeks after treatment

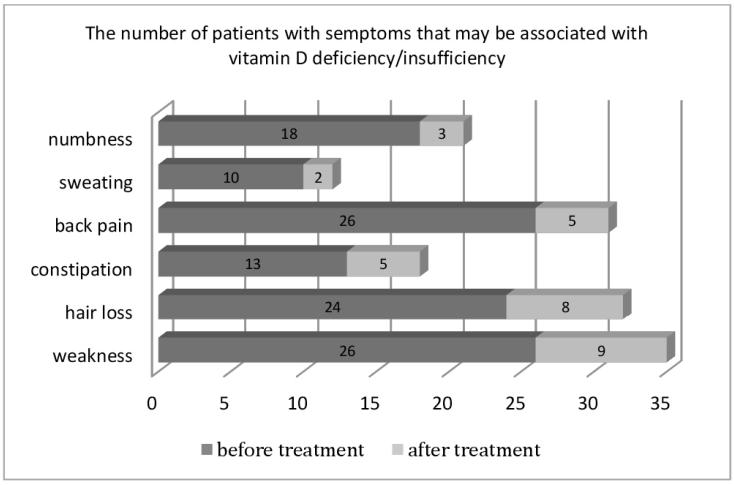
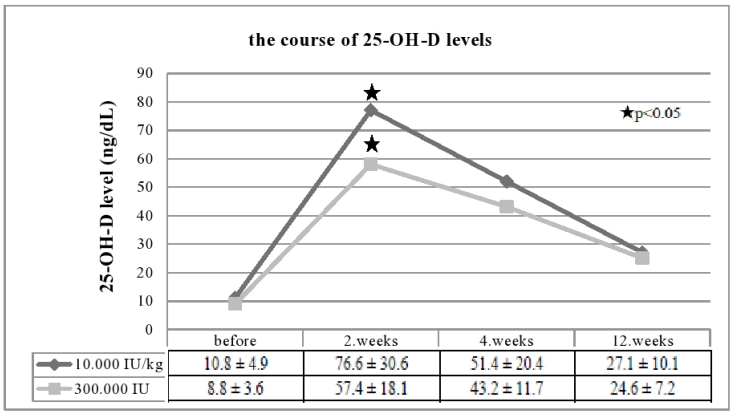


Figure 2: Two different high-dose treatment protocols and the course of 25-OH-D levels with time



	before	2.weeks	4.weeks	12.weeks
10.000 IU/kg	10.8 ± 4.9	76.6 ± 30.6	51.4 ± 20.4	27.1 ± 10.1
300.000 IU	8.8 ± 3.6	57.4 ± 18.1	43.2 ± 11.7	24.6 ± 7.2