Evaluating the effectiveness of various Vitamin D formulations after 8 weeks of treatment

Abstract:

Background:

Vitamin D hasa vital starring role in bone metabolism which also promotes the absorption of calcium in the intestine. Thus, adequate level of vitamin D is of critical importance. Methods:A prospective, randomized, comparative, parallel-group study evaluated the effectiveness, safety and tolerability of three Vitamin D3 products in patients with vitamin D3 deficiency or insufficiency. These products included soft gelatin capsule, granules, and chewable tablet. Thedosing regimen was once a week for eight weeks. Change in levels of 25-hydroxyvitamin D and calcium were analyzed.Results:The change in 25-hydroxyvitamin D levels from baseline to week 8, and the results of paired t-test indicated statistically significant rise in 25-hydroxyvitamin D levels in each group. The mean percentage improvement in 25-hydroxyvitamin D was in the order: chewable tablet>capsule>granules. The chewable tablet showed an additional important benefit of highest rise in calcium levels, and the rise was in the order: chewable tablet>capsule>granules. Furthermore, no adverse event was noted in any group. Conclusion:The effectiveness of the chewable tablet in improving both 25-hydroxyvitamin D and calcium levels along with the cost-effectiveness, ease of use, and palatability makes it an attractive choice over other oral formulations in treatment of patients with 25-hydroxyvitamin D insufficiency or deficiency.

Keywords- Calcium, efficacy, supplementation, vitamin d3, 25- hydroxyvitamin D

Introduction

Vitamin D, a group of sec steroids comprising vitamin D2 (ergocalciferol) and D3 (cholecalciferol), has a vital role in Phosphorous and calcium metabolism and maintenance of healthy immune system[1, 2, 3]. Exposing the skin to ultraviolet B rays leads to vitamin D3 production from 7-dehydrocholesterol; the dietary sources provide both vitamin D2 and D3. In the liver, vitamin D2 and D3 are converted to a prohormonecalcidiol (25-hydroxyvitamin D). The measurement of 25-hydroxyvitamin D isthe best method to diagnose the vitamin D status of a person [2, 4]. Vitamin D and its metabolites also have

numerous clinical applications, including its effectiveness in rickets, hyperparathyroidism, pseudo hypothyroidism, renal osteodystrophy, osteoporosis(steroid-induced, postmenopausal, senile), anticonvulsant drug-induced osteomalacia, hepatic disorders, depression, cancer, obesity, heart disease, Parkinson's disease, influenza, bacterial vaginitis, and many others [5-8]. Vitamin D is primarily involved in promoting the absorption of calcium from the intestine by inducing the formation of calcium binding proteins causing demineralization of bones [1, 9].Calcium is essential to maintain strong bones and perform vital functions, including supporting the structure and hardness of teeth and bones, movement of muscles, and transfer of messages between the brain and the body via nerves. It also supports the supply of blood to the body and release of hormones and enzymes affecting every function in the human body [10]. Although calcium is an abundantly found mineral in variety of foods, its absorption in the body requires vitamin D and deficiency of vitamin D may impact health causing muscle weakness, skeletal fragility, and several non-skeletal diseases [1,9,10]. Thus, vitamin D supplementation is a recommended safe and effective method for those who do not get enough exposure to the sun or are vitamin D deficient [11, 12].As the production of vitamin D in the skin is influenced by factors, such as clothing, time of the day, latitude, altitude, age, pigmentation, and use of sunscreen, deficiency is highly prevalent worldwide, including India. It is also because of the limited dietary sources of vitamin D, and fortification is optional but inconsistent, insufficient, or nonexistent, causing a large population to rely on production of vitamin D in the skin [2, 11, and 13]. Thus, we can consider supplementation as an effective method. Supplementation of vitamin D3 can be through various oral products; however, the absorption varies based on the dosage form used. In addition, nanotechnology is an effective way to improve the absorption, and thus, improves the bioavailability of oral vitamin D3 [4]. Thus, we included a product made with nanotechnology, the chewable tablet, in our study. Although several oral dosage forms of vitamin D3 are available in the market, there is no published literature comparing the effectiveness and safety of granules, chewable tablets, and capsules in a single study [4]. Therefore, we aimed to evaluate and compare the effectiveness, safety, and tolerability of different vitamin D3 products, including granules, chewable tablets, and capsules, in adults with 25-hydroxyvitamin D deficiency or insufficiency.

Methods:

This prospective, randomized, comparative, open-label, parallel-group study evaluated the effectiveness, safety and tolerability of threeVitamin D3 products. Ethics Committee approval was obtained prior to initiating the study andgood clinical practice guidelines as applicable was followedduring the entire study period.

1)Screening and eligibility criteria. All the patients aged ≥18 years who were –not participating inany other clinical trial during the study. Patients with –calcium level <8 mg/dL or >10.5 mg/dL at baseline; 25-hydroxyvitamin D <10 ng/mL or >30 ng/mL at baseline; hypersensitivity to the study treatment history of chronic disease; current significant acute or chronic illness; pregnancy and lactation; no tolerability to oral medications; use of glucocorticosteroids, anticonvulsants, anti-tubercular, diuretic, and cholesterol-lowering drug therapy in previous three months; prior diagnosis of cancer and current treatment with radiation, chemotherapy, or immunotherapy; a risk of being exposed to sun during the study;a recent tour to the beach or experienced sun bath; dependency on drug or alcohol within one year prior to screening; or circumstance that could compromise the integrity of the study data or affect the analyses if the disease exacerbates during the study or place the subject at risk by participating in the study, in the opinion of the investigator, were excluded from participating in this study.

2)Randomization was performed by using block randomization technique by generating a list of numbersin a statistical program. Patients were randomizedin equal ratio to the three treatment groups to include approximately 15 patients in each group

3)Treatment groups and dosing regimen. The three treatments in the study included vitamin D3 60K internationalunits (IU) and were:

- Treatment A: Uprise D3 soft gelatin capsule (of Alkem Laboratories)
- Treatment B: Calcirol granules (of Cadila Pharmaceuticals)

•Treatment C:Gen D3 Nano chewable tablet (of Macleods Pharmaceuticals).

4)Statistical analysisStatistical analysis was performed on intent to treat (ITT) population using Statistical Analysis System® (SAS®), (SAS Institute Inc., Cary, USA) Version 9.4 or higher. ITT population included all randomized patients who were enrolled in the study and received at least one dose of the allocated study treatment. Statistical test was performed at 5% level of significance. Analyses were done by 2-sided 5% level of significance for both primary and secondary endpoint. ANOVA was used for between treatment group comparisons and paired test was used for within treatment group comparison of parameters.5)Primary effectiveness analysisThe mean change in 25-hydroxyvitamin D from baseline (day 1 of week 1) to endpoint, i.e., week 8 (post-dose) was analyzed.6)Secondary effectiveness analysis. The mean change in serum calcium from baseline (day 1 of week 1) to week 8 (post-dose) was analyzed.

Results:

This study included adult men and women with normal mean BMI of 25.03 kg/m2. The mean age of the patientsincluded in this study was 33.98 years.1)Patient disposition. One patient receiving chewable tablet and one patient receiving granules were withdrawn from the study on their own accord after 3rd and 5th dose, respectively. Among those who completed the study, one patient receiving granules did notreport to the facility for dosing of week 3.2)Rising Trend in 25-hydroxyvitamin D levels. The mean 25-hydroxyvitamin D levels indicated a rise in all the treatment groups at each week during the 8 week treatment period, except at week 5. As per the laboratory range for vitamin D, <10 ng/mL indicates deficiency, 10 to 30 ng/mL indicates insufficiency, 30 to 100 ng/mL indicates sufficiency and >100 ng/mL indicates hypervitaminosis D. The baseline and week 8 values of mean 25-hydroxyvitamin Din our study are demonstrated in Table 1. At week 3, all the products except granule demonstrated a vitamin D level > 30 ng/mL, i.e., sufficiency range. Patients in all the treatment groups achieved sufficiency band of vitamin D at week 8. Although the numerical values suggest that capsule had a higher value than chewable tablet, the percentage rise was significantly higher in Chewable tablet. (Table 1 and Figure 1).

3)Primaryeffectiveness endpoint.The mean percentage change in 25-hydroxyvitamin D levels from baseline (day 1 of week 1) to week 8 (post-dose), and the results of within treatment comparison by paired t-test in each treatment group indicated statistically significant change in 25-hydroxyvitamin D levels in each treatment group.

Table 1.

1) Mean percentage change in 25-hydroxyvitamin Dlevels form baseline to week 8

Vitamin D360K IU Products	N	Mean 25-hydroxyvitamin D levels (mg/mL)		Mean differences	Change in %	P-value
		Baseline	Week 8			
Chewable tablet	13	14.54	57.62	43.058±11.60	296.30	0.000000014134
Soft Gelatin Capsule	14	16.47	62.21	45.74±18.10	277.71	0.000000342682
Granules	11	14.2	40.68	26.48±10.34	186.49	0.000006933862

Table 2 Mean percentage change in 25-hydroxyvitamin Dlevels after week 8

Vitamin D360K IU Products	N	Mean 25-hydroxyvitamin D levels (mg/mL)		Mean differences	Change in %	P-value
		Baseline	Week 8			
Chewable tablet	13	8.92	9.43	0.5±0.58	5.77	0.007451
Soft Gelatin Capsule	14	8.86	9.17	0.30±0.53	3.43	0.053356
Granules	11	9.1	9.19	0.09±0.36	1.02	0.411832

The percentage change in 25-hydroxyvitamin D levels at week 8 was found to be in the order: chewable tablet>capsule>granules. Chewable tablet was found to have a significantly higher probability of changes in 25-hydroxyvitamin D levels from baseline to week 8 than capsule and granule formulations. (Table 1 and Figure 1).

4)Secondaryeffectiveness endpoint. The mean serum calcium level in each treatment group was assessed at baseline and at each week during the 8-week treatment period (Figure 2). Although rise in calcium level was observed with all the treatments used in our study, only chewable tablet demonstrated statistically significant rise in calcium levels (Table 2, Figure 2, and Figure 3).

5)Safety endpoint. No adverse events were reported in any of the treatment groups throughout the study period, and all the products used were safe and tolerable.

Discussion:

All the vitamin D3 products used in our study showed significant rise in levels of 25-hydroxyvitamin D. Chewable tablet has high probability of changes from baseline to week 8 than capsule and granule formulations. In our study, capsule (62.21 ng/mL), chewable tablet (57.62 ng/mL), and granules (40.68 ng/mL) showed improvements within the safe range that will not lead to vitamin D toxicity or hypervitaminosis D, a condition characterized by hypercalcemia, hypercalciuria, and elevated vitamin D>150 ng/ml. The mean percentage improvement in 25-hydroxyvitamin D was in the order: chewable tablet>capsule>granules. The risein calcium level was in the order: chewable tablet>capsule>granules. Vitamin D is primarily involved in promoting the absorption of calcium from the intestine by inducing the formation of calcium binding proteins causing remineralization of bones [1, 9].This was demonstrated in our study, wherein chewable tablet showed highest rise in calcium levels after vitamin D3 supplementation.Chian CM et al., 2016, conducted a systematic review of six published papers to identify the effects of vitamin D supplementation on muscle strength in athletes. Vitamin D3 was administered

in four studies and vitamin D2 was administered in the other two studies. The duration of the study and dose were from 6 weeks to 4 months and 400 to 8,500 IU per day, respectively. The results indicated that vitamin D2 may be ineffective in improving muscle strength. However, vitamin D3 supplementation may improve muscle function parameters. Vitamin D3 supplementation led to improvements in muscle strength or significant improvements in the outcome measure [14]. Thus, it supports the use of vitamin D3 as a relatively more effective supplementation for vitamin D than vitamin D2. Reid IR et al., 2013, published a systematic review and meta-analysis, including all randomized trial available at the time of publication, reporting the effectiveness of vitamin D supplementation on bone mineral density. The meta-analysis demonstrated that there could be small benefit at femoral neck through vitamin D supplementation [15]. Another meta-analysis of randomized controlled trial estimated the effects of vitamin D3 supplementation in prevention of hip and non-vertebral fractures. A daily dose of 700 to 800 IU lowered the relative risk of hip fracture and non-vertebral fracture by 26% and 23%, respectively. However, a daily oral dose of 400 IU is inadequate to prevent fractures [16]. Thus, the published literatures demonstrate the role of vitaminD3 supplementation in improving muscle strength and reducing the risk of fractures which is possibly related to the rise in calcium levels as vitamin D is involved in calcium metabolism. Our study is in line with the available literatures indicating the effectiveness and safety of different formulations of vitamin D3 and varying levels of 25-hydroxy vitamin D achieved in each group at the end of study.

Fig. 1 Mean percentage change in 25-hydroxyvitamin D levels form baseline to week 8

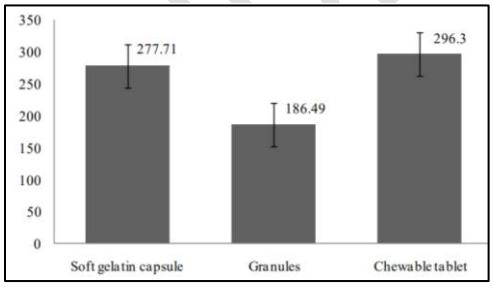


Fig. 2 Mean serum calcium levels (mg/dL) in each treatment group (vitamin D3 60K IU) during the study period.

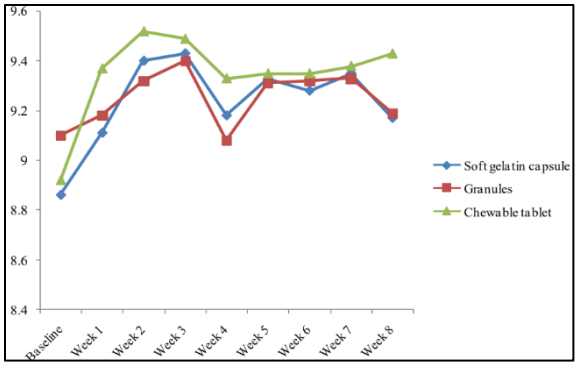
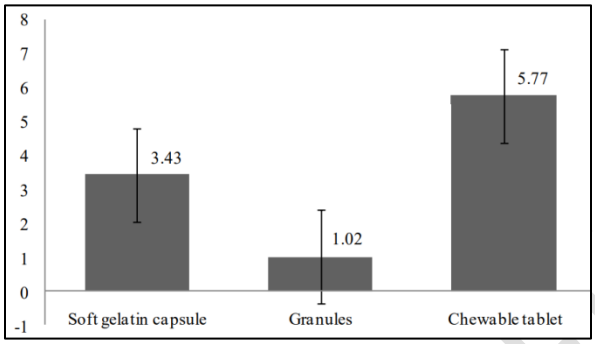


Fig.3 Mean percentage change in calcium levels form baseline to week 8



Conclusion:-

Vitamin D3 supplementation is an effective way to prevent and manage several health conditions as well as to maintain healthy bones. The maximum percentage rise in 25-hydroxy vitamin D level was noted with chewable tablet followed by capsule and granules, respectively. Statistically significant rise in calcium level was noted only withchewabletablet. The chewable table is formulated using nanotechnology, indicating the role of nanotechnology in increasing the 25-hydroxyvitamin D and calcium absorption from the formulation. Chewable tablet, along with rise in vitamin D3, showed additional important benefit of highest rise in calcium levels; the cost-effectiveness, palatability, and patient-friendliness of chewable tablet over other formulations in the study may be considered as advantageous factors for patient compliance in treating vitamin D deficiency or insufficiency.

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