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# Efficacy and Safety of Vitamin D 3 (Cholecalciferol) Oral Solution Compared to Tablet and Capsule: A Randomized, Parallel-Design, Active-Controlled Study

Dr. Prashant J. Palkar

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## Abstract

We performed a study to compare the efficacy of Vitamin D3 oral solution with a conventional tablets and capsules in hypovitaminosis D patients. One hundred eighty subjects were divided into three different groups and received vitamin D3 60000 IU per week for eight weeks either in the form of an oral solution or a tablet or a capsule. A significant increase in serum 25(OH)D was observed in vitamin D3 oral solution from baseline (P=0.0001) as compared to a tablet (P=0.0001) and capsule (P=0.0001). A significant decrease in iPTH levels was seen in the vitamin D3 oral solution group from baseline (P=0.0001) and also as compared to a tablet (P=0.0001) and capsule (P=0.0001). Oral solution of vitamin D3 is a nanotechnology-based formulation which was found to be effective and safe. Thus, treatment with vitamin D3 oral solution in hypovitaminosis D patients may result in faster and higher improvement in the normalization of vitamin D levels.

***Index terms***— nanotechnology, hypovitaminosis D, vitamin D3 oral solution, vitamin D3 60000 IU.

## 1 Introduction

he prevalence of hypovitaminosis D indicates that it is a common and notable problem worldwide, as identified in numerous epidemiological studies (1). Environmental factors, such as increased air pollution and reduced ultraviolet B (UVB) irradiation, as well as lifestyle factors, i.e., decreased outdoor activities and less intake of vitamin D-rich food, are likely involved in the etiology of a dramatic reduction of vitamin D circulating levels (2). The insufficiency and deficiency of vitamin D raises public health concern since it is independently associated with a higher risk of all-cause mortality (3,4). Hypovitaminosis D has long been known to increase the risk for osteoporosis and rickets. Only in the last decades, it has been linked with various chronic pathological conditions, i.e., cancer, coronary heart disease (CHD), non-insulin dependent diabetes, neurological disorders, as well as autoimmune and inflammatory diseases (5,6). The community-based Indian studies of the past decade done on apparently healthy controls reported a prevalence ranging from 50% to 94% (7). increase in serum 25(OH)D was observed in vitamin D 3 oral Treatment with either vitamin D 2 (ergocalciferol) or vitamin D 3 (cholecalciferol) has been recommended for vitamin D deficient patients (8). Nevertheless, as per evidence, vitamin D 3 are superior at raising serum 25(OH)D concentrations than vitamin D 2 , and thus vitamin D 3 could potentially become the preferred choice for supplementation (9). Vitamin D is a fatsoluble vitamin and it has a poor bioavailability, which significantly reduces its efficacy as disease-combating agent (10). Oral dosage forms like tablet, capsule, and oral solutions have different absorption rates. The efficiency of oral absorption of conventional vitamin D 3 is approximately 50% (11). In general, the availability for the absorption of a drug is more in oral solutions comparing to the capsule and tablet, respectively (12). In accordance to this, our previous bioequivalent study conducted in healthy volunteers, in which we had first time compared three different formulations (tablet, capsule, and oral solution) of vitamin D 3 and proved that the C max and AUC of an oral solution of vitamin D 3 are higher than that of the tablet and capsule (13). The aim of the present study is to compare and assess the efficacy of oral solution of vitamin D 3 with that of tablets and capsules in

hypovitaminosis D patients. Furthermore, this is the first study to our knowledge to compare three different formulations of vitamin D in hypovitaminosis D subjects.

# 2 a) Study Design

The present study was a multi-centre, parallelgroup, active-controlled study to evaluate the safety and efficacy of vitamin D 3 oral solution Hi-D TM

# 3 b) Subjects

Total 180 subjects, male and female, were enrolled in this study with the mean age of 43.9±16.63 years (minimum -19 years and maximum -89 years). The inclusion criteria for participants were that they should be >18 years of age at the time informed consent was obtained, have subnormal serum 25(OH)D levels on screening, female patients with negative urine or serum pregnancy test within seven days before baseline visit. Participants were excluded if they were with clinical signs or symptoms of overt metabolic bone disease such as bone pains, myopathy or fractures; with history of GI malabsorption, abnormal liver, renal or heart function, or underwent gastrointestinal surgeries in the past; suffering from hypocalcemia or hyperparathyroidism; have hypersensitivity to vitamin D.

Patients were randomized in 3 equal groups of vitamin D 3 oral solution, vitamin D 3 tablet, and vitamin D 3 capsule, respectively. All three groups received 60000 IU of vitamin D 3 per week for eight weeks in the form of respective formulation. Out of 180 patients, 164 completed the study comprising 55 patients in each vitamin D 3 oral solution Hi-D TM (Akumentis Healthcare Limited, Mumbai) and D 3 MUST TM 60K (Mankind Limited, India) group and 54 patients in Uprise-D 3 60K ® group (Alkem Limited, India).

# 4 c) Outcomes

Primary outcomes included efficacy of vitamin D 3 formulations, which were evaluated by comparing and assessing all three formulations on attaining vitamin D sufficiency (serum 25 (OH) D levels) at the end of treatment (8 weeks) to find out differences between vitamin D formulations. Secondary outcomes include changes in intact parathyroid activity (serum iPTH levels) at the end of treatment (8 weeks) in all the groups. Safety was evaluated by assessing and comparing all three formulations on changes in serum calcium, serum phosphorous, serum alkaline phosphatase, serum albumin, and serum creatinine levels at the end of treatment (8 weeks) and reported adverse events during the study till the end of treatment (8 weeks) in all the groups to find out differences between vitamin D formulations. Adverse Events (AEs) were categorized by investigators according to their intensity as Grade 1-mild, Grade 2-moderate, or Grade 3-severe. Patients were encouraged to report AEs spontaneously or in response to a general non-directed questionnaire.

# 5 d) Statistical Analysis

Descriptive statistical methods were used to summarize demographic, baseline characteristics, and all other analysis variables. Data was presented in terms of mean +/-SD and range for all variables. All patients were compared at baseline for homogeneity using analysis of variance (ANOVA) as appropriate Paired ttest was used for comparison. Statistical analysis was performed on the per-protocol (PP) population which included the subjects who had completed the study without any significant protocol deviation. Two-sided tests were used with $P<0.05$ being considered significant.

# 6 III.

# 7 Results

All the patients enrolled in this study were Asian; the baseline demographic data are shown in Table 1. In primary outcomes, the serum 25(OH)D levels with vitamin D 3 oral solution Hi-D TM group were elevated more than three times compared to baseline in the 8 th week. This increase in 25(OH)D levels by oral solution was significant as compared to the tablet and capsule group from the baseline to the 8 th week (Figure 1). The iPTH levels in vitamin D 3 oral solution were suppressed significantly by 63.53% as compared to tablet and capsule group from the baseline to the 8 th week (Figure 2).

Secondary outcomes were similar in all three groups after treatment (Table 2). There was no serious adverse event reported in the overall study period. No patient developed vitamin D toxicity. Six cases of nonlaboratory related AEs were reported and were mild in intensity.

# 8 Discussion

The status of vitamin D depends on the production of vitamin D and vitamin D intake through the diet or vitamin D supplements. Owing to its fat-soluble nature, dietary vitamin D is absorbed with other dietary fats in the small intestine. The efficient absorption of vitamin D is dependent upon the presence of fat in the lumen, which triggers the release of bile acids and pancreatic lipase. In turn, bile acids initiate the emulsification of lipids, pancreatic lipase hydrolyzes the triglycerides into monoglycerides and free fatty acids, and bile acids support the

formation of lipid-containing micelles, which diffuse into enterocytes (14). In India, a current recommendation for correction of vitamin D level is by giving 60,000 IU of oral vitamin D every week for eight weeks (15).

Different dosage forms are produced to achieve the appropriate absorption through the suitable form of the drug as different drugs require different routes of administration. Absorption of each substance occurs differently by the human body. Hence different administration routes, as well as dosage forms, are provided and recommended for each substance under which the dose of the drug will be absorbed, delivered, and distributed more effectively. When it comes to oral dosage forms, solutions are one of the preferable dosage forms. Their strongest advantage is based on the fast and high absorption of soluble medicinal products. Solutions are one of the "leading" dosage forms due to their application in patients with swallowing difficulties and their easy administration (16).

The use of nanotechnology in formulation development and lifecycle management can make drug development significantly cost-effective. Also, nanotechnology can target specific drugs, which can reduce toxicity and improve efficacy. Nanotechnologybased delivery systems can also protect drugs from degradation (17). Several studies of nanotechnologybased formulations of vitamins like vitamin A and vitamin E reported significant improvement in the plasma levels of the vitamins after the administration of the formulation (18,19). V.

# 9 Conclusion

Vitamin D 3 60000 IU oral solution appears to be better and faster treatment option for improving vitamin D levels as compared to tablets and capsules. Moreover, the nanotechnology-based formulation of an oral solution of vitamin D 3 increases plasma vitamin D levels rapidly, and it is also found to be safe. Thus, vitamin D 3 oral solution may be a better alternative than the tablet and capsule formulations in hypovitaminosis D subjects.

The use of nanoparticle-based Vitamin D oral solution is increasing in the market. The bioavailability of nutrients that have poor water solubility can be increased by nanotechnology (11,20). Evidence showed that nanoparticles of vitamin D 3 might also enhance important properties of vitamin D supplements, like therapeutic efficacy, photo-stability, and biodegradation (21). Moreover, in our previous study, we have compared the bioequivalence of vitamin D 3 oral solution with that of conventional vitamin D 3 tablets and capsules. We observed that the oral solution of vitamin D has higher C max and AUC as compared to tablet and capsule (13).

In this study, we have evaluated the efficacy and safety of 3 different formulations of vitamin D 3 (oral solution, tablet, and capsule) in subjects with hypovitaminosis D. Results were in favour of oral solution as serum vitamin D level was increased significantly and reached up to the normal level. This result was significantly better as compared to tablets and capsules. Serum iPTH level was also improved significantly in oral solution as compared to tablets and capsules.

Manek K observed that nanoparticle-based formulation of vitamin D 3 is effective and safe in the correction of vitamin D levels in patients with documented deficiency or insufficiency of vitamin D (15). Similar results were found by Marwaha et al., documenting vitamin D 3 oral solution achieves significantly higher levels of serum 25(OH)D (18). These evidence substantiate our findings with similar observation.

To the best of our knowledge, this is the first study comparing the efficacy and safety of [1]

Figure 1: Figure 1 :

Figure 2: Figure 2 :

Figure 3:

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Council on Harmonization of requirements for registration of pharmaceuticals for human use-Good Clinical Practice (ICH-GCP).
The study protocol (version no.: 01 dated 19 December 2018) and the informed consent form in English (version no.: 01 dated 26 December 2018) &
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Global Journal of containing vitamin D 3 60000 IU of Akumentis Healthcare Limited, India (oral solution group) comparing with two reference products, D 3 MUST TM 60K, a tablet containing vitamin D 3 60000 IU of Mankind Limited (tablet group), and Uprise-D 3 60K ® , a capsule containing vitamin D 3 60000 IU of Alkem Limited, India (capsule group) in patients with hypovitaminosis D. This study was performed from 9 April 2019 to 13 September 2019.
The study was carried out in compliance with the protocol by current local legislation, International
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Figure 4:

**1**

| Variable | Vit D 3 Oral Solution (N=60) | Vit D 3 Tablet (N=60) | Vit D 3 Capsule (N=60) | All Enrolled (N=180) |
|---|---|---|---|---|
| Age (Years) Mean (SD) Min, Max | 42.7 (16.54) 20.0, 76.0 | 42.7 (18.52) 19.0, 89.0 | 46.18 (14.64) 23.0, 81.0 | 43.9 (16.63) 19.0, 89.0 |
| Gender Male Female | 35 25 | 36 24 | 29 31 | 100 80 |
| Height (cm) Mean (SD) Min, Max | 162.8 (4.17) 154, 171 | 162.8 (4.36) 155, 174 | 164.0 (3.64) 155, 171 | 163.2 (4.09) 154, 174 |
| Weight (Kg) Mean (SD) Min, Max | 69.1 (10.79) 47, 87 | 69.0 (9.61) 51, 88 | 71.1 (10.32) 48, 90 | 26.21 (4.07) 47, 90 |
| BMI (Kg/m 2 ) Mean (SD) Min, Max | 26.11 (4.36) 17.10, 34.90 | 26.04 (3.65) 19.0, 32.0 | 26.49 (4.24) 18.9, 35.2 | 26.21 (4.07) 17.10, 35.2 |

IV.

Figure 5: Table 1 :

**2**

| Treatments | Vit D 3 nano oral solution (N=55) | Vit D 3 tablet (N=55) | Vit D 3 capsule (N=54) |
|---|---|---|---|
| Calcium (mg/dL) Baseline Week 8 | 9.28 9.40 | 9.32 9.31 | 9.42 9.40 |
| Serum Phosphorus (mg/dL) | 3.51 | 3.71 | 3.70 |
| Baseline | 3.67 | 3.64 | 3.59 |
| Week 8 | | | |
| Alkaline Phosphatase (IU/L) | 290.87 | 291.98 | 284.61 |
| Baseline | 244.96 | 277.05 | 271.71 |
| Week 8 | | | |

Figure 6: Table 2 :

## .1 Acknowledgement

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## .2 Conflict of Interest

None declared

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