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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

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I. Introduction

The 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).

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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 fat-soluble 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.

II. Methods

a) Study Design

The present study was a multi-centre, parallel-group, active-controlled study to evaluate the safety and efficacy of vitamin D_3 oral solution Hi-D™ containing vitamin D_3 60000 IU of Akumentis Healthcare Limited, India (oral solution group) comparing with two reference products, D_3 MUST™ 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

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) & Marathi (version no.: 01 dated 31 December 2018) languages were used for obtaining written informed consent from each of the subjects were approved by the Ethics Committee on 27 February 2019, i.e., before the commencement of the study.

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™ (Akumentis Healthcare Limited, Mumbai) and D_3 MUST™ 60K (Mankind Limited, India) group and 54 patients in Uprise-D_3 60K® group (Alkem Limited, India).

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.

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 t-test 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.

III. 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™ group were elevated more than three times compared to baseline in the 8th 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 8th 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 8th 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 non-laboratory related AEs were reported and were mild in intensity.

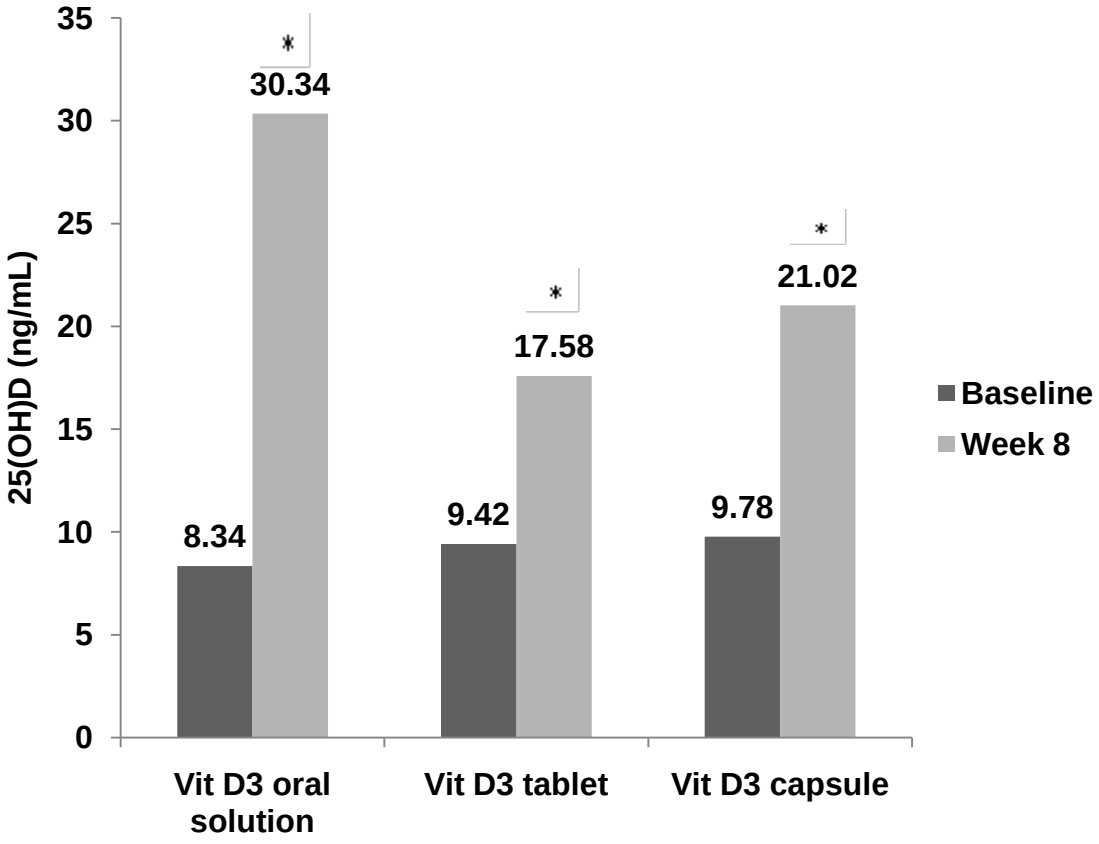

Figure 1: Change in serum 25(OH) D level at the end of eight weeks in all three treatment groups (n = 164). *P=0.0001 vs baseline; †P=0.0001 vs Tablet and Capsule.

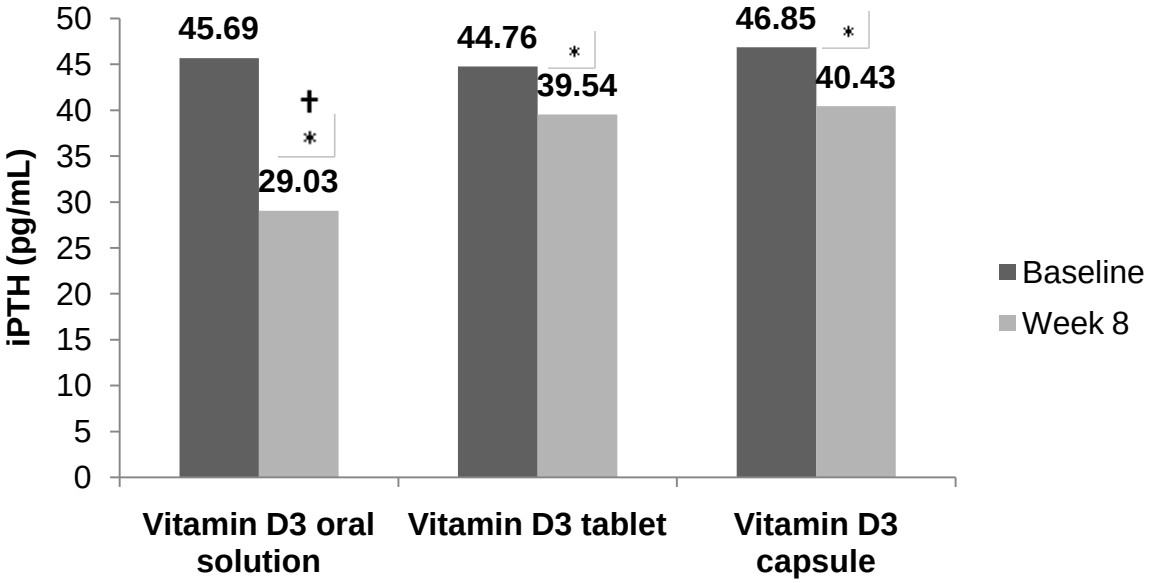

Figure 2: Change in serum iPTH levels at the end of eight weeks in all three treatment groups (n = 164). *P=0.0001 vs baseline; †P=0.0001 vs Tablet and Capsule.

Table 1: Overall demographic profile of all subjects (N = 180)

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. 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. Nanotechnology-based delivery systems can also protect drugs from degradation (17). Several studies of nanotechnology-based 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).

Table 2: Changes in serum parameters (N=164)

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) Baseline Week 8	3.51 3.67	3.71 3.64	3.70 3.59
Alkaline Phosphatase (IU/L) Baseline Week 8	290.87 244.96	291.98 277.05	284.61 271.71

Serum Albumin (g/dL) Baseline Week 8	4.30 3.40	4.35 4.30	4.45 4.35
Serum Creatinine (mg/dL) Baseline Week 8	0.79 0.83	0.78 0.76	0.79 0.74
Treatments	Vit D_3 nano oral solution (N=55)	Vit D_3 tablet (N=55)	Vit D_3 capsule (N=54)

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 3 different formulations of vitamin D_3 (oral solution, tablet and capsule) in subjects with hypovitaminosis D.

V. Conclusion

Vitamin D_3 60000 IU oral solution appears to be a 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.

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Conflict of Interest

None declared

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