



## A comparative study of two marketed preparations of Vitamin D for safety and efficacy in Vitamin D deficient children

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### Abstract

**Aim and Objectives:** The present study was undertaken to compare the safety and efficacy of two Vitamin D syrups in normalizing various biochemical markers of Vitamin D deficiency in children.

**Method:** 79 children of either sex, aged between 8 to 15 years were enrolled in the study. They were divided into two groups to receive either one of the two marketed formulations of Vitamin D3. 36 patients were treated with Uprise D3 [Syrup (A)] and 43 patients were treated with Deksel nano syrup (B). Both formulations containing 60,000 IU of Cholecalciferol were administered once a week for 10 weeks. The change in 25(OH) D levels from baseline was recorded at 6 weeks and 12 weeks.

**Results:** Both the formulations have shown a significant rise in 25(OH) D levels but the rise with Syrup B was significantly higher than that seen with Syrup A over baseline, at week 6 and week 12. Treatment with either of the formulations was able to reduce the elevated alkaline phosphatase levels both at 6 and 12 weeks. But in neither of the case reduction from the baseline was significant. Serum calcium and serum phosphorus levels remained unaltered after either of the treatment, both at 6 and 12 weeks. Significant reduction in elevated parathyroid hormone levels was seen only with Deksel nano syrup. This was observed as early as 6 weeks of initiating treatment.

**Conclusion:** Deksel nano syrup is a better formulation as it was shown to produce consistently higher rise in 25(OH) D levels. The formulation also demonstrated a trend towards normalization of elevated parathyroid hormone levels.

**Keywords:** Vitamin D, Uprise D3 Syrup, Deksel nano syrup, Cholecalciferol, Alkaline phosphatase, Parathyroid hormone.

### Introduction

Vitamin D is essential for maintaining calcium homeostasis and optimizing bone health. Calcitriol (1,25-Dihydroxyvitamin D), the active

vitamin D metabolite, binds to a specific nuclear hormone receptor thereby increasing intestinal calcium absorption and regulating bone turnover<sup>[1]</sup>. Low concentrations of vitamin D lead

to alterations in calcium and phosphorus homeostasis, secondary hyperparathyroidism, bone loss, osteoporosis, and an increase in fracture risk in adults and in children. Severe degrees of vitamin D deficiency lead to impairment of bone mineralization and rickets. The standard method of assessing vitamin D status is by measuring serum concentration of its major circulating metabolite 25-hydroxyvitamin D [25(OH) D]<sup>[2]</sup>.

Numerous epidemiological studies have assessed the prevalence of low serum 25(OH) D concentrations and have indicated that vitamin D inadequacy is a common problem worldwide. Differences in the prevalence of vitamin D inadequacy have been related to a variety of factors, including physiological changes with age, race, body mass index (BMI), sun exposure, latitude, and dietary intake<sup>[3]</sup>. Opinions regarding the optimal concentration of serum 25(OH) D vary widely. Several studies have shown that serum concentrations of at least 20–30 ng/ml are necessary to maximize intestinal calcium absorption and minimize perturbations in PTH, calcium, and phosphorus homeostasis<sup>[3]</sup>.

Furthermore the differential absorption parameters of various types of oral vitamin D preparations are yet to be understood completely.

Pulse Pharmaceuticals is a technology driven pharmaceutical company. They have recently introduced in the market their nano-particle vitamin D syrup, Deksel, which has been developed using patented Aqueol Technology. This formulation is believed to give faster and greater rise in vitamin D levels compared to other marketed formulations. The purpose of this study was to objectively evaluate the safety and efficacy of this nano-syrup in overcoming the vitamin D deficiency in children and at the same time, comparing its efficacy with the other marketed formulations.

### Materials and Methods

This single centre, randomized, two arm study was conducted at the Paediatric OPD of LTMMC and LTMGH Sion, Mumbai, after obtaining the

requisite approval from Institutional Ethics Committee (IEC) and written informed consent from the parent or legally acceptable representative (LAR) as per the local requirements. Inclusion criteria also included that the subject and parent/ legally acceptable representative are able to attend all scheduled visits and to comply with all trial procedures.

Total 164 children attending paediatric OPD, were screened for vitamin D deficiency and those found deficient as per US Endocrine Society criteria (Table 1), reproduced hereunder, were enrolled in the study. Total 79 vitamin D deficient children of either gender, age between 8 to 15 years, were included in the study and divided into two groups to receive either one of the two marketed formulations. 36 patients received Uprise D3 Syrup (A) and 43 patients received Deksel nano syrup (B). Both formulations containing 60,000 IU of Cholecalciferol were administered once a week for 10-weeks. The change from baseline of 25(OH) D levels was recorded at 6-weeks and 12-weeks.

**Table 1:** Vitamin D Status in Relation to 25(OH) D Levels<sup>[4]</sup>

Vitamin D Status	Levels
Deficiency	<20 ng/ mL
Insufficiency	21 – 29 ng/ mL
Sufficiency	>30 ng/ mL
Toxicity	>150 ng/ mL

The exclusion criteria of the study were given below

1. Participation in another clinical trial in the 4 weeks preceding the trial inclusion or planned participation during the present trial period in another clinical trial investigating a drug, vaccine, medical device, or medical procedure.
2. Known or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy, such as anticancer chemotherapy or radiation therapy since birth; or on long-term systemic corticosteroid therapy.

3. Known hypersensitivity to any of the formulation components, or history of a life threatening reaction to the trial medication containing the same substances.
4. Known thrombocytopenia, as reported by the parent/ legally acceptable representative.
5. Bleeding disorder or receipt of anticoagulants in the 3 week preceding inclusion.
6. Chronic illness that, in the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion. (Chronic illness may include but is not limited to, cardiac, renal, autoimmune, hepatic, haematological, genetic disorders, atopic conditions, congenital defects, diabetes, convulsions or encephalopathy etc.).
7. Moderate or severe acute illness/ infection (according to investigator judgment) on the day of inclusion (a prospective subject should not be included in the study until the condition has resolved or the event has subsided).
8. Identified as a natural or adopted child of the Investigator, relatives or employee

with direct involvement in the proposed study.

### Statistical Analysis

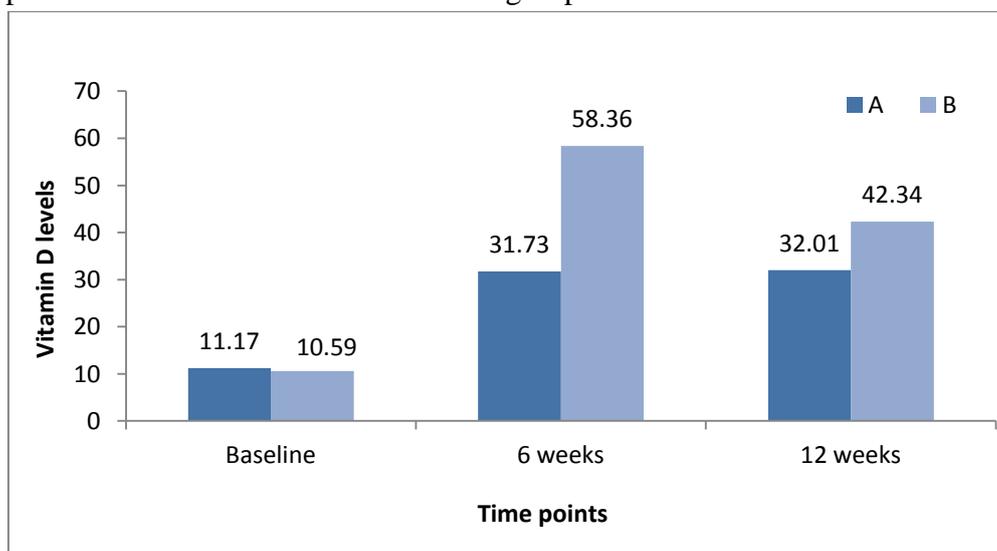
Data were analyzed using SPSS statistical package. Data were given as Mean±SD for numerical data. Student's unpaired t-test was applied to compare means between 2 groups. Student's paired t-test was used to compare change between 2 time points separately for each group. All statistical tests were 2 tailed.  $P \leq 0.05$  was taken as significant.

### Observations and Results

A total 79 children were enrolled in the study out of which 36 patients were treated with Uprise D3 Syrup. Of these 36 patients, 7 patients were lost to follow-up. Deksel nano syrup was prescribed to 43 patients and out of these, 14 patients were lost to follow-up. So the final number of patients included for analysis in each group was 29.

The comparison of mean change in vitamin D level between two groups is depicted in Figure 1. Both the formulations have shown a significant rise in 25(OH) D levels over baseline at week 6 and week 12. The rise with Deksel nano syrup was significantly higher than that seen with Uprise D3 syrup ( $P < 0.001$ ). There was significant difference for all changes observed in Vitamin D (time point-Basal) as shown in table 2.

**Figure 1:** Comparison of mean Vitamin D between 2 groups



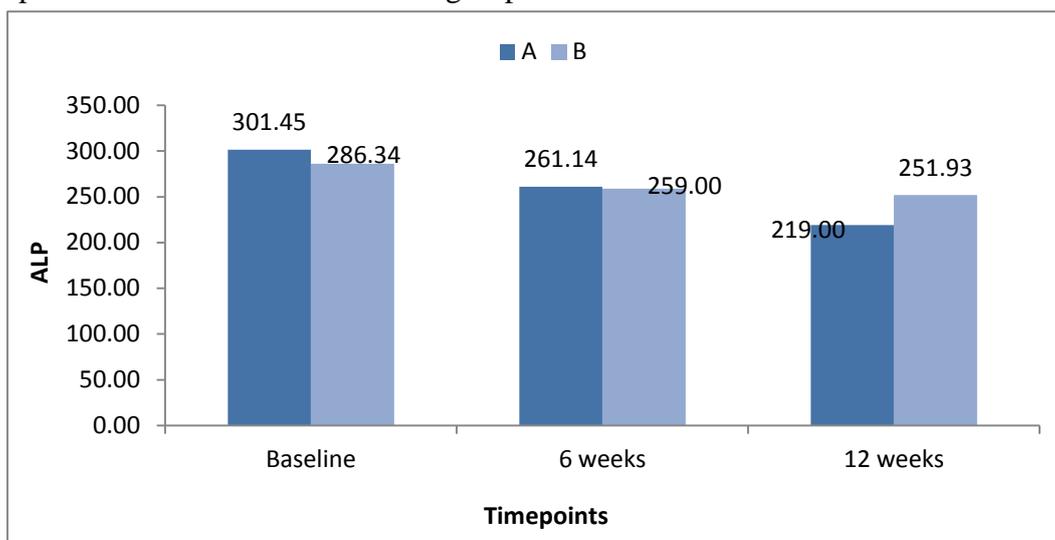
**Table 2:** Comparison of mean difference in Vitamin D between 2 groups

Drug Treatment	25(OH)D levels in ng/ml		
	6 weeks-Baseline	12 weeks-Baseline	12 weeks-6 weeks
A	20.56 ± 12.50	20.84 ± 17.60	0.27 ± 19.06
B	47.77 ± 27.45	31.75 ± 19.94	(-)16.02 ± 28.29
A vs. B	t=4.9,S,P<0.001	t=2.2,S,P=0.03	t=2.6,S,P=0.013

Treatment with either of the formulations i.e., Uprise D3 and Deksel nano syrup was able to reduce the elevated alkaline phosphatase (ALP) levels both at 6 weeks and 12 weeks. But in

neither of the case the reduction from baseline was significant, (Figure 2). There was no significant difference for all changes in ALP (time point-Basal) as shown in table 3.

**Figure 2:** Comparison of Mean ALP between 2 groups



**Table 3:** Comparison of mean difference in ALP between 2 groups

Drug Treatment	6 weeks-Baseline	12 weeks-Baseline	12 weeks-6 weeks
A	41.64 ± 109.58 (n=28)	91.43 ± 138.71 (n=28)	44.74 ± 87.93 (n=27)
B	30.80 ± 79.35 (n=25)	38.50 ± 83.71 (n=25)	10.54 ± 64.08 (n=26)
A vs. B	t=4.9,S,P<0.001	t=2.2,S,P=0.03	t=2.6,S,P=0.013

Serum calcium and phosphorus levels remained unaltered after either of the treatment, both at 6 weeks and 12 weeks. There was no significant

difference between A and B except at baseline. (Table 4).

**Table 4:** Comparison of Mean serum Calcium and mean serum Phosphorus between 2 groups

Drug Treatment	Baseline	6 weeks	12 weeks
<b>Comparison of Mean serum Calcium between 2 groups</b>			
A	8.96 ± 0.83 (29)	9.17 ± 0.99 (28)	8.99 ± 0.68 (27)
B	9.05 ± 0.95 (26)	9.14 ± 0.67 (25)	9.08 ± 0.74 (25)
A vs B	t=0.5,NS,P=0.6	t=0.1,NS,P=0.9	t=0.5,NS,P=0.6
<b>Comparison of mean serum Phosphorus between 2 groups</b>			
A	4.58 ± 0.66 (29)	5.11 ± 0.81 (29)	4.86 ± 0.82 (29)
B	4.99 ± 0.59 (28)	5.25 ± 0.53 (29)	5.20 ± 0.45 (29)
A vs B	t=2.8,S,P=0.013	t=0.8,NS,P=0.4	t=1.9,NS,P=0.052

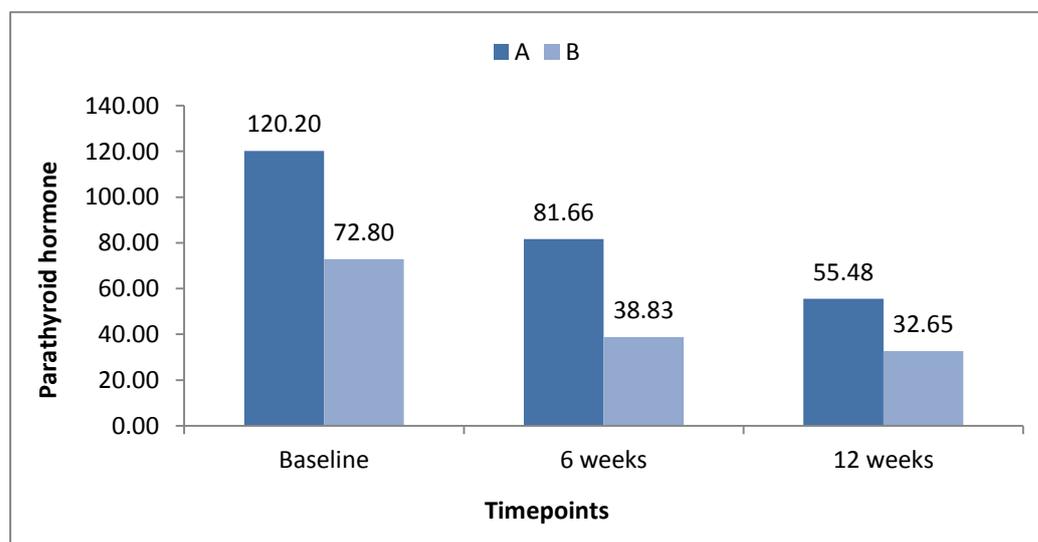
A significant reduction in elevated parathyroid hormone levels was seen with both the treatments.

Reductions in parathyroid hormone levels became evident much earlier i.e., at week 6 with Deksel

nanosyrup, whereas with Uprise nanosyrup the reduction was apparent at 12 weeks. We found significant difference between A and B except at

Basal level as shown in figure 3. Comparison of mean Parathyroid hormone between 2 time-points for each group is depicted in table 5.

**Figure 3:** Comparison of mean change in parathyroid hormone between 2 groups



**Table 5:** Comparison of mean Parathyroid hormone between 2 time-points for each group

Drug Treatment (Paired t test)	Baseline	6 weeks	12 weeks
A	120.20 ± 135.45	81.66 ± 110.65	55.48 ± 53.30
Between Baseline & 6 weeks	t=3.9,S,P=0.001		
Between 6 weeks & 12 weeks	t=2.1,S,P=0.04		
B	72.80 ± 57.28	38.83 ± 28.26	32.65 ± 19.04
Between Baseline & 6 weeks	t=4.0,S,P<0.001		
Between 6 weeks & 12 weeks	t=1.9,NS,P=0.07		

## Discussion

Vitamin D deficiency (VDD) is a major health problem in both the developed and developing countries across the globe. In India despite ample sunlight (required for the synthesis of vitamin D endogenously), VDD prevalence has been documented to be in range of 50-90% among all the age groups<sup>[5]</sup>. It is important in children mainly because of its profound effect on growth and development. Since approximately 40%-60% of total skeletal mass at maturity is accumulated during childhood and adolescence, it has major implications on adult bone health. It regulates calcium and phosphorus balance for bone mineralization and remodeling<sup>[6]</sup>.

In the present study, which included children in the age range from 8 to 15 years, we found a 48.17% prevalence of VDD in children attending

Paediatric OPD of LTMMC and LTMGH Sion, Mumbai, India. Mandlik et al<sup>[7]</sup> noted that, in school children ( $n = 359$ ) aged 6–12 years from a semirural government-run primary school, only 5% had sufficient levels of 25-hydroxy vitamin D [25(OH) D levels >75 nmol/L] and the rest had either vitamin D deficiency (VDD) (24%) or insufficiency (71%), despite majority of children (80%) reporting sunlight exposure of  $\geq 2$  hours. Similarly, a study by Marwaha et al<sup>[8]</sup> in school children from Delhi between 10 to 18 years of age found that over one third had 25(OH)D values <9 ng/ml. Basu S et al<sup>[9]</sup> reported 72.1% vitamin D deficient children in their study done in a pediatric hospital in eastern part of India i.e. Kolkata. Few studies from north India demonstrated that the prevalence of VDD in apparently healthy children is as high as 90%<sup>[8,10,11]</sup>. The differences observed

in the prevalence of VDD among healthy children in different studies could be due to the different populations studied, latitude of residence, sunlight exposure, skin color, environmental pollution and weather, vitamin D intake (diet and supplementation), different methods used to measure 25(OH) D, and different cut-off values<sup>[11]</sup>.

Considering the increased prevalence of VDD and the confusion about supplementation and treatment of vitamin D deficiency for various age groups, the Indian Academy of Pediatrics has recently published a set of recommendations for prevention and treatment of vitamin D and calcium deficiency in July 2017<sup>[12]</sup>.

**Table 6:** Prevention and treatment in vitamin D deficiency<sup>[12]</sup>

Age	Prevention	Tolerable* Upper Limit	Treatment	Treatment with large dose (oral route preferred)
Premature Neonates	400 IU/day	1000 IU/day	1000 IU/day	NA
Neonates	400 IU/day	1000 IU/day**	2000 IU/day	NA
1-12 months	400 IU/day	1000-1500 IU/day**	2000 IU/day	60000 IU weekly for 6 weeks (over 3 months of age)
1-18 years	600 IU/day	3000 IU/day till 9 years, 4000 IU/day from 9-12 years. <sup>2</sup>	3000-6000 IU/day	60000 IU weekly for 6 weeks
At risk groups	400-1000 IU/day	As per age group	As per age group	As per age group

\*Tolerable Upper Limit - the maximum level of total chronic daily intake of a nutrient (from all sources).<sup>2</sup> For a minimum of 3 months; after treatment, daily maintenance doses need to be given.

Various preparations are available in India for the treatment of vitamin D deficiency such as Vitamin D3 – as oral drops 400 IU/mL; Uprise D3 oral syrup; Syrup 400 IU/5mL; and Tablets as 1000 and 2000 IU in blister packing. It is also available as sachets in powder form with each sachet containing 60000 IU of vitamin D3<sup>[13]</sup>. Recently Pulse Pharmaceuticals have introduced their nano-particle vitamin D syrup, Deksel, which has been developed using patented Aqueol Technology. In the current study, we evaluated the safety and efficacy of this nano-syrup in overcoming vitamin D deficiency in children while simultaneously comparing it with the other marketed formulation i.e. Uprise D3 syrup. The results illustrate that the rise in 25(OH)D levels with Deksel nano syrup was much greater than what was achieved with Uprise D3 syrup. Significant reduction in elevated parathyroid hormone levels was seen only with Deksel nano syrup. This was observed as early as 6 weeks of treatment. A trend towards

normalization of elevated Alkaline Phosphatase was evident with both the treatments but a significant reduction was not achieved in either of the groups. With the dosing schedule used, no changes in serum Calcium and serum Phosphorus were evident. None of the Subjects reported any adverse events with either of the formulations. Both the formulations were equally tolerated well.

### Conclusion

Both tested formulations i.e., Uprise D3 syrup and Deksel nano syrup were found to be efficacious in raising 25(OH) D levels in 8-15 year old Vitamin D deficient children. But Deksel nano syrup produced consistently higher rise in 25(OH) D levels and also demonstrated a trend towards normalization of elevated parathyroid hormone levels. Therefore in our opinion Deksel nano syrup is a better formulation as compared to Uprise D3 syrup.

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Sponsored: Yes

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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