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Comparative Efficacy of Oral vs. Intramuscular Cholecalciferol in Treating Severe Vitamin D Deficiency

[1]Shashank Prakash, [2]Hima Chauhan, [3]Rajnand Kumar, [4]Nitish Kumar and [5]Ajay Bharti

[1,3,4,5]Department of Orthopaedics, All India Institute of Medical Sciences, Gorakhpur, India

[2]Critical Care Medicine, Fortis-Escorts Heart Institute, New Delhi, India

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Corresponding Author
Hima Chauhan
Critical Care Medicine, Fortis-Escorts Heart Institute, New Delhi, India
himnet20@gmail.com

Author Designation
[1,2]Senior Resident
[3,4]Associate Professor
[5]Professor

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ABSTRACT

Vitamin D insufficiency is a widespread global health issue, significantly impacting skeletal and neuromuscular health. Despite its prevalence, vitamin D deficiency often goes unrecognized due to its subtle symptoms. While oral vitamin D supplementation is a common treatment, patient adherence is often poor, leading to the exploration of alternative treatment modalities, such as high-dose intermittent vitamin D therapy. This prospective, randomized, open-label study was conducted on 80 adults with severe vitamin D deficiency, defined by serum 25(OH)D levels below 30 ng/mL. Participants were randomly assigned to two groups: one received oral cholecalciferol (60,000 IU every other day for 20 days) and the other received a single intramuscular (IM) injection of cholecalciferol (600,000 IU). Serum levels of 25(OH)D, PTH, calcium, phosphorus and alkaline phosphatase (ALP) were measured at baseline, 6 weeks and 12 weeks to assess the efficacy of the treatments. Both treatment groups showed significant improvements in serum 25(OH) D levels. The intramuscular group exhibited a more consistent and sustained increase in 25(OH)D levels compared to the oral group. PTH levels decreased significantly in both groups, with no significant differences between them. Calcium and ALP levels remained stable, with minor variations that were not clinically significant. Both oral and intramuscular cholecalciferol are effective in treating severe vitamin D deficiency. However, intramuscular administration may offer a more consistent and sustained increase in 25(OH)D levels. Further research is needed to compare the long-term efficacy and safety of these two treatment modalities in larger, more diverse populations.

INTRODUCTION

Vitamin D insufficiency is being acknowledged as a prevalent medical problem worldwide[1]. Vitamin D is crucial for the development of the skeletal system, maintaining bone health and ensuring the functioning of the neuromuscular system. Due to the subtle or vague nature of the signs and symptoms of vitamin D deficiency, it is frequently not identified or treated.

Frank vitamin D deficiency is defined as having a level of 25(OH)D below 10 ng per milliliter (ng/ml). It is a well-known medical condition that is marked by muscle weakness, bone discomfort and fragility fractures. Vitamin D insufficiency is defined as having a level of 25(OH)D between 10 and 30 ng/ml, while a level of 30 ng/ml or higher is considered ideal[3].

The evaluation of the prevalence of vitamin D deficiency/insufficiency is hindered by the varying threshold levels employed in different research. Vitamin D deficiency is prevalent among senior individuals living in communities in nations located at higher latitudes. It is even more widespread among elderly individuals living in institutions, geriatric patients and patients with hip fractures[4].

Elderly individuals are more susceptible to vitamin D deficiency due to limited sunlight exposure, reduced ability of aging skin to produce vitamin D and inadequate consumption of dietary vitamin D[5]. At least 50% of[6] older individuals residing in residential homes are expected to have a deficiency in vitamin D, with claimed prevalence rates as high as 75%[7].

Research has demonstrated a connection between a lack of Vitamin D and muscle weakness in individuals of different age groups, an increased risk of losing balance in individuals with osteoporosis or prone to falling and a higher likelihood of falls in older individuals living in institutions[8]. Research examining the impact of vitamin D supplementation and the relationship between low levels of 25(OH)D and physical performance yield inconclusive findings. Several research have demonstrated the positive impact of Vitamin D supplementation on muscle strength, physical performance and the prevention of falls[9,10]. However, there are other studies that have not found any evidence of increased muscle strength with Vitamin D supplementation[11-13].

The adherence to oral vitamin D supplementation is typically poor[14-16]. Only 50% of postmenopausal women with osteoporosis who take calcium and/or vitamin D adhere effectively to this treatment[14]. Many patients had difficulty swallowing big tablets and effervescent tablets containing calcium might cause gastrointestinal adverse effects[17]. The concept of administering high-dose intermittent vitamin D treatment emerged as a result of inconsistent adherence to calcium and vitamin D replacement medication. In Turkey, the national health insurance system covers the cost of vitamin D in the form of oral drops, high-dose ampoules, or effervescent pills combined with calcium. Due to the potential gastrointestinal and cardiovascular adverse effects of calcium[18], we are hesitant to prescribe combination effervescent formulations in a safe manner.

Multiple studies have examined the pharmacokinetics, biochemical effects, effectiveness and safety of administering a single high-dose of cholecalciferol. These studies have shown that this approach is safe, well-tolerated and effective[6,11,17,19,20].

The main objective of this study is to assess Efficacy of Single dose im vitamin d3 60 Lacs IU vs alternate day 60k IU for 20 days in severe vitamin d3 deficiency patient.

MATERIALS AND METHODS

This was a prospective, randomized, open label single institution study in which 80 adults with Vitamin D deficiency were studied. The subjects were in good condition and did not show any obvious signs of vitamin D deficiency or other metabolic bone disorders. They willingly agreed to participate in the study protocol. Vitamin insufficiency was characterised by serum 25OHD levels below 30 ng/mL. The study excluded subjects with any condition that is known to impact mineral metabolism. The study excluded individuals with any chronic medical conditions and those who were on chronic medications. Prior to recruitment, the study subjects were provided with a written consent form and their agreement was obtained. The study was also authorised by the Ethics Committee. A total of eighty participants with a pronounced shortage of Vitamin D were enlisted. A total of 80 patients were randomly assigned to two groups: 40 subjects received oral cholecalciferol every other day, while the other 40 subjects received a single intramuscular injection of cholecalciferol. Baseline and 6-and 12-week blood samples were taken during the intervention. During each visit, the levels of serum calcium (adjusted for albumin), phosphorus, alkaline phosphatase (ALP), 25OHD and intact parathyroid hormone (iPTH) were determined. The levels of serum calcium, phosphorus and ALP were assessed on the same day. The sera for 25OHD and PTH were held at a temperature of-40 degrees Celsius until they were measured. The chemiluminescence method was used to determine the serum iPTH. The radioimmunoassay method was used to determine the Serum 25OHD.

RESULTS AND DISCUSSIONS

Table 1 presents the baseline characteristics of the study population, comparing the oral and higher in the

oral group (25.14 kg/m²) compared to the intramuscular group (23.35 kg/m²). Baseline 25(OH)D levels were lower in the oral group (5.99 ng/mL) than in the intramuscular group (7.40 ng/mL). The intramuscular group had higher baseline PTH levels (69.92 pg/mL) compared to the oral group (52.82 pg/mL). Calcium and phosphorus levels were similar across both groups, while alkaline phosphatase levels were slightly higher in the intramuscular group (182.80 IU/L) compared to the oral group (166.73 IU/L).

Table 1: Baseline Characteristic of the Study Population

	Oral cholecalciferol group	Intramuscular cholecalciferol group
Age	28.45±5.29	29.75±6.31
Gender (male: female)	14:26	14:26
BMI (kg/m2)	25.14±2.46	23.35±2.99
25(OH) D (ng/ml)	5.99±1.07	7.40±1.13
PTH (pg/ml)	52.82±8.51	69.92±8.92
Calcium (mg/dl)	10.01±0.15	10.09±0.15
Phosphorus (mg/dl)	3.97±0.11	3.93±0.11
Alkaline phosphatase (IU/L)	166.73±7.424	182.80±7.79

Table 2 compares the changes in 25-hydroxyvitamin D (25(OH)D) and other biochemical parameters before and after the intervention between the oral and intramuscular cholecalciferol groups. At baseline, the intramuscular group had slightly higher 25(OH)D levels (7.40 ng/ml) compared to the oral group (5.99 ng/ml). After 12 weeks, 25(OH)D levels significantly increased in both groups, but the intramuscular group showed a greater increase (25.46 ng/ml) compared to the oral group (16.66 ng/ml), with significant differences noted at the 12-week mark ($p<0.001$).

For parathyroid hormone (PTH), the intramuscular group had higher baseline levels (69.92 pg/ml) than the oral group (52.82 pg/ml). Both groups showed significant reductions in PTH over time, with no significant differences between them at 12 weeks.

Calcium levels decreased slightly in both groups by 6 weeks but increased by 12 weeks, with similar patterns observed across the groups. Phosphorus and alkaline phosphatase (ALP) levels remained stable, with ALP showing a significant decrease in the intramuscular group over time ($p=0.027$). Overall, the intramuscular group exhibited a more pronounced and sustained improvement in 25(OH)D levels compared to the oral group.

*Mixed effect regression model was applied to test the difference in change of mean (25(OH) D, PTH, calcium and ALP) values over time between both the groups, #Repeated measure one way ANOVA was applied to test the change in mean (25(OH) D, PTH, calcium and ALP) values over time. PTH: Parathyroid hormone, 25(OH) D: 25 hydroxyvitamin D, ALP: Alkaline phosphatase.

There is a significant amount of uncertainty over the correct approach to treating Vitamin D insufficiency. The situation is worsened by the fact that there are numerous formulations of Vitamin D3 available (oral and parenteral) and there is no universally acknowledged method for replenishing it. This study assessed the impact of administering Vitamin D3 through different methods (oral vs. intramuscular) on the levels of serum 25OHD in persons who are apparently healthy but have Vitamin D insufficiency. Both intervention groups demonstrated an enhancement in serum 25OHD levels upon completion of the research. Nevertheless, the group receiving intramuscular cholecalciferol demonstrated a notable increase in 25OHD levels in comparison to the group receiving oral cholecalciferol.

The average blood 25OHD level at the beginning of the study in the group taking oral cholecalciferol was 7.40±1.13 ng/mL. After 6 weeks, it jumped to 20.20±1.65 ng/mL, but subsequently reduced to 16.66±1.36 ng/mL after 12 weeks. Whyte *et al.* demonstrated that the concentrations of 25-hydroxyvitamin D increase rapidly and reach their highest point approximately one week after administration. However, this peak is not maintained if supplementation is discontinued or if the maintenance dosage is not initiated[21]. The average 25OHD level at the beginning of the study in the IM D3 group was 5.99±1.07 ng/mL and it grew throughout time.

The concentration of the substance increased to 20.74±1.81 ng/mL at 6 weeks, which is almost three times higher than the initial value. It further increased to 25.46±1.37 ng/mL at 12 weeks, which is nearly four times higher than the initial value. In this group, approximately six participants out of a total of 20 reached levels exceeding 30 ng/mL, whereas eight participants out of 20 reached a level of 20 ng/mL. The average blood 25OHD levels remained consistently below 30 ng/mL in both the oral and intramuscular cholecalciferol groups.

The average serum levels of 25OHD attained after 6 weeks were similar in the oral cholecalciferol and IM intramuscular cholecalciferol groups. Both groups were similar in age, with a mean age of 28.45 years in the oral group and 29.75 years in the intramuscular group. The gender distribution was identical, with 14 males and 26 females in each group. The BMI was slightly cholecalciferol groups. However, after 12 weeks, the IM cholecalciferol group exhibited a higher 25OHD level (25.46±1.37 vs. 16.66±1.36). Mawer *et al.* have hypothesized that orally administered Vitamin D binds to lipoproteins and is transported to the liver, where it

Table 2: 25 Hydroxy Vitamin D and Other Parameters Before and After Intervention

	Oral cholecalciferol (n=40)	Intramuscular cholecalciferol (n=40)	P Difference for each time point (t test: Oral vs. intramuscular)	Mixed effect regression model (oral vs. intramuscular)*
25(OH) D (ng/ml)				
Baseline	5.99±1.07	7.40±1.13	0.332	<0.001
6 weeks	20.20±1.65	20.74±1.81	0.853	
12 weeks	16.66±1.36	25.46±1.37	<0.001	
Repeated measure one way ANOVA#	P<0.001	P<0.001		
PTH (pg/ml)				
Baseline	52.82±8.51	69.92±8.92	0.335	0.473
6 weeks	25.39±9.01	34.59±9.57	0.761	
12 weeks	12.83±8.66	12.16±8.72	0.876	
Repeated measure one way ANOVA#	P<0.001	P=0.004		
Calcium (mg/dl)				
Baseline	10.01±0.15	10.09±0.15	0.567	0.680
6 weeks	8.97±0.19	9.07±0.20	0.774	
12 weeks	9.57±0.18	9.90±0.18	0.413	
Repeated measure one way ANOVA#	P=0.001	P=0.001		
ALP (IU/L)				
Baseline	166.73±7.42	182.80±7.79	0.243	0.271
6 weeks	167.53±8.45	157.73±8.99	0.427	
12 weeks	149.11±8.21	148.56±8.21	0.947	
Repeated measure one way ANOVA#	P=0.137	P=0.027		

undergoes metabolism by hepatic 25-hydroxylase and some of it is deactivated. This can elucidate the larger yet more temporary rises in serum 25OHD levels following a single oral administration of cholecalciferol[22]. Our findings align with previous research that has compared two distinct methods of Vitamin D administration. Cipriani *et al.* demonstrated that an oral dose of 600,000 IU of vitamin D2 or D3 is more efficient in initially raising serum 25OHD levels compared to an equivalent intramuscular dose. Additionally, this oral dose is quickly digested[23]. The depot intramuscular (IM) preparation is deposited at the injection site, resulting in a gradual and prolonged release[21].

Zabihiyeganeh *et al.* showed that two distinct oral and injectable treatment plans, both using a total dose of 300,000-IU Vitamin D3, were highly effective and safe in treating hypovitaminosis[24]. The researchers determined that oral preparations are efficient in correcting Vitamin D insufficiency in the short-term. In our investigation, the serum 25OHD levels at 6 weeks were similar in both the oral and intramuscular (IM) D3 groups. Leventis and Kiely conducted a comparison between oral and intramuscular (IM) regimes for replacing Vitamin D3 in patients with Vitamin D deficiency. The regimes consisted of a single dosage of 300,000 IU[25]. The researchers determined that administering a 300,000-IU dose of either Vitamin D2 or D3 was safe, well-tolerated and led to a consistent increase in serum 25OHD levels and effective suppression of PTH. Diamond *et al.* demonstrated the safety and efficacy of a yearly intramuscular injection of 600,000 IU cholecalciferol, which successfully restored normal levels of 25OHD in all patients and maintained levels above 50 nmol/L for the duration of the trial[26]. Tellioglu *et al.* showed that in older individuals with Vitamin D deficiency/insufficiency, a large single dosage of cholecalciferol substantially raised Vitamin D levels and most of the patients achieved optimum levels[27]. By the conclusion of the research, all patients in the IM group had blood 25OHD levels of $\geq$30 ng/mL, while 83.3% of the patients in the oral group had the same level.

Research has shown that adherence to oral Vitamin D supplementation is typically inadequate[28,29]. For individuals who have a serious problem with absorbing nutrients or who may not be taking their oral medication as directed, it is recommended to receive an intramuscular injection of 300,000 IU of calciferol once a month for 3 months and then continue with the same amount once or twice a year as a different treatment option[30]. Administering a single dosage of injectable Vitamin D is expected to enhance patient adherence. In India, this will also be economically advantageous, as the cost of a single injection of Vitamin D is roughly equivalent to the cost of one sachet of Vitamin D, which is administered once a week. This can impose a substantial economic strain in a country such as India, particularly among the lower socioeconomic group, where all members of a family may necessitate medical attention. The pharmacokinetics of intramuscular (IM) administration

of vitamin D3 and its absence of oscillations in 25-hydroxyvitamin D (25OHD) levels make it a good therapeutic choice for patients with obesity, malabsorption and those who have difficulties with treatment adherence[31]. Nevertheless, the administration of excessively high doses and the imprudent utilization of the parenteral route may be linked to complications, including hypercalcemia, hypercalciuria and Vitamin D toxicity[32]. Two extensive community-based randomized controlled studies, comparing the effects of yearly dosages of Vitamin D with a placebo, found that the group receiving Vitamin D supplements had higher rates of fractures[33,34].

The authors hypothesized that the improved mobility observed after the large annual dose of Vitamin D may be due to high serum levels of Vitamin D or its metabolites, followed by a decline in these levels. However, they also suggested that the persistence of a mineralization defect could increase the risk of fractures[34].

Individuals suffering from Vitamin D deficiency frequently have increased levels of intact parathyroid hormone (iPTH). The average PTH level in this study did not show a significant increase, even though there was a severe deficit of Vitamin D (69.92±8.9 pg/mL vs. 52.83±8.5 pg/mL). Nevertheless, the PTH readings fell within the upper end of the normal range and may be deemed elevated given the age of the participants[35]. Both arms exhibited a statistically significant decrease in PTH levels compared to the initial measurement. Multiple studies have indicated that certain individuals may not have an increase in parathyroid hormone (PTH) levels above the usual upper limit, despite having low levels of vitamin D (hypovitaminosis D)[36,37]. The absence of parathyroid hormone (PTH) increase in numerous patients with low levels of circulating 25OHD has been extensively discussed, however no definitive answers have been identified.

The present investigation has specific limitations. The subjects were not kept unaware of the treatment, and the duration of follow-up was limited. A more extensive follow-up could have provided a more accurate description of the progression or improvement of 25OHD levels throughout time. While we did not assess individuals for hypercalciuria by measuring urine calcium levels, recent studies conducted in India and Turkey have not found any notable hypercalciuria in participants who received Vitamin D treatment[38,39].

CONCLUSION

Both oral and intramuscular (IM) administration modalities are equally effective in treating Vitamin D insufficiency. The group receiving cholecalciferol in the intramuscular (IM) form exhibited a consistent and lasting rise in serum 25OHD levels compared to their initial levels. Further research is required to thoroughly evaluate the advantages and disadvantages of the oral and intramuscular administration methods. This should involve a bigger randomized control trial with a higher dosage and a longer period of observation.

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