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COMPARISON OF ORAL VERSUS INTRAMUSCULAR VITAMIN D THERAPY FOR CHILDREN WITH VITAMIN D DEFICIENCY

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Abstract

Objective:

To compare oral vitamin D therapy and intramuscular vitamin D therapy in terms of mean increase in vitamin D levels in children with vitamin D deficiency.

Material and Methods:

In this randomized controlled trial, a total of 220 patients with diagnosed vitamin D deficiency were included. Patients were then randomized to one of two groups via block randomization (the allocation was done through Manila envelopes): Group A received oral vitamin D therapy, while Group B received intramuscular vitamin D therapy. All patient were tested for serum calcium, phosphate, alkaline phosphatase and serum 25 hydroxy vitamin D levels at baseline i.e., before administration of treatment. Patients were followed up at three-, six- and twelve-weeks post-initiation of therapy and tested for serum calcium, phosphate, alkaline phosphatase and serum 25 hydroxy vitamin D levels at these intervals.

Results:

The mean age was 6.52 ± 1.95 years in Group A and 6.54 ± 1.97 years in Group B ($p = 0.93$). The gender distribution was also similar, with males comprising 57.7% (75/130) in Group A and 56.9% (74/130) in Group B ($p = 0.9$). Over the course of the study, Group A consistently exhibited a greater mean increase in serum vitamin D levels compared to Group B at all follow-up intervals. At three weeks, the mean increase in vitamin D levels was 3.15 ± 1.17 ng/mL in Group A, significantly higher than the 1.61 ± 0.28 ng/mL observed in Group B ($p < 0.0001$). At six weeks, Group A's mean increase rose to 10.82 ± 2.12 ng/mL, while Group B's mean increase was 7.83 ± 1.41 ng/mL ($p < 0.0001$). By twelve weeks, the mean increase reached 16.0 ± 2.99 ng/mL in Group A compared to 10.9 ± 3.17 ng/mL in Group B ($p < 0.0001$).

Conclusion:

Oral vitamin D is superior to intramuscular therapy in treating vitamin D deficiency in children.

INTRODUCTION

Vitamin D, a secosteroid hormone, plays a crucial role in maintaining musculoskeletal health. Its deficiency has become alarmingly widespread, resembling a pandemic. Lack of this essential

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nutrient has been associated with the development of autoimmune conditions, certain cancers, and ischemic heart disease, among various other health issues.[1] During periods of rapid growth, such as infancy and adolescence, insufficient vitamin D may manifest as hypocalcemia, reflecting unmet bodily demands. Severe deficiency can lead to conditions like rickets and cause symptoms such as seizures or muscle tetany.[2] Additionally, vitamin D deficiency has long-term implications for children, contributing to illnesses like cystic fibrosis, asthma, chronic obstructive pulmonary disease, and interstitial lung disease. It is also linked to the onset of hypertension and diabetes in the pediatric population.[3, 4]

Given the crucial role of vitamin D in supporting the growth and upkeep of a healthy human body, addressing vitamin D deficiency is of utmost significance. Several treatment protocols have been suggested, differing in dosage, administration frequency, and the use of ongoing maintenance therapy. One approach, known as Stoss therapy, involves administering a single, large dose of vitamin D. While this method has been described in some detail for adult patients, there is a lack of sufficient data regarding its effectiveness.[5, 6] Furthermore, it remains uncertain whether administration via injection is necessary or if an oral dose would suffice.[6] The aim of this study was to compare oral vitamin D therapy and intramuscular vitamin D therapy in terms of mean increase in vitamin D levels in children with vitamin D deficiency.

METHODS:

This randomized controlled trial was carried out in the Department of Pediatrics at a tertiary care hospital from January 2024 to December 2024. We enrolled patients between the ages of 3 and 10 years who were diagnosed with vitamin D deficiency. Participants were excluded if they had used any form of vitamin D supplementation within the past three months, or if they had malabsorption syndromes such as Celiac disease or Whipple's disease. Additional exclusion criteria included chronic pancreatitis, cystic fibrosis, chronic liver or kidney disorders, or recent use (within six months) of medications that could affect vitamin D absorption and metabolism, such as antituberculosis agents, antiepileptic drugs, or corticosteroids. Patients with a history of allergic reactions to vitamin D, whether oral or intramuscular, were also excluded.

Patients provided demographic information and underwent a thorough clinical history and examination at the time of their inclusion in the study. Subsequently, they were randomly assigned to one of two groups using block randomization with allocation concealed in manila envelopes. Group A was given oral vitamin D supplementation, whereas Group B received intramuscular vitamin D injections. The oral group was administered a one-time dose of 300,000 IU of vitamin D3 orally, followed by daily supplementation of calcium at 50 mg/kg and vitamin D at 400 IU for twelve weeks. In contrast, the intramuscular therapy group received a single intramuscular injection of 600,000 IU of vitamin D3, then continued with daily oral calcium and vitamin D supplements at the same doses for the same duration. Baseline blood tests were conducted for all participants, measuring serum calcium, phosphate, alkaline phosphatase, and 25-hydroxyvitamin D levels prior to treatment. Follow-up assessments were performed at three, six, and twelve weeks after starting therapy, with repeated testing of serum calcium, phosphate, alkaline phosphatase, and 25-hydroxyvitamin D at each interval.

Patients were documented for age, gender, height, weight, and serum calcium, phosphate, alkaline phosphatase, and serum 25-hydroxy vitamin D levels at baseline as well as at three-, six-, and twelve-weeks, and the mean increase in Vit-D levels was determined.

SPSS Version 26 was used for data analysis. An independent sample t-test was applied to compare the mean increase in vit. D levels between the groups considering p-value ≤0.05 as significant difference.

RESULTS:

The baseline characteristics of the two study groups, Group A and Group B (each with 110 participants), were comparable. The mean age was 6.52 ± 1.95 years in Group A and 6.54 ± 1.97 years in Group B ($p = 0.93$). The gender distribution was also similar, with males comprising 57.7% (75/130) in Group A and 56.9% (74/130) in Group B ($p = 0.9$), while females accounted for 42.3% and 43.1% in Groups A and B, respectively. Baseline laboratory

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investigations showed that serum calcium levels were 9.91 ± 0.6 mg/dL in Group A and 9.93 ± 0.58 mg/dL in Group B (p = 0.72). Serum phosphate was 1.49 ± 0.11 mmol/L in Group A and 1.48 ± 0.12 mmol/L in Group B (p = 0.63). Alkaline phosphatase levels were 223.87 ± 9.35 IU/L in Group A and 222.35 ± 8.30 IU/L in Group B (p = 0.20). Serum vitamin D levels were 15.30 ± 2.6 ng/mL in Group A and 15.68 ± 2.4 ng/mL in Group B (p = 0.28) (Table 1).

At the 12-week follow-up, laboratory investigations revealed similar results between Group A and Group B except vit. D levels. The mean serum calcium level was 11.29 ± 1.23 mg/dL in Group A and 11.23 ± 1.21 mg/dL in Group B (p = 0.71), indicating no significant difference. Serum phosphate levels were also comparable, with Group A recording 1.63 ± 0.19 mmol/L and Group B 1.61 ± 0.18 mmol/L (p = 0.43). Alkaline phosphatase levels were 247.86 ± 6.36 IU/L in Group A versus 247.28 ± 6.29 IU/L in Group B (p = 0.49). However, there was a statistically significant difference in serum vitamin D levels, with Group A showing a higher mean value of 31.3 ± 1.48 ng/mL compared to 26.6 ± 1.81 ng/mL in Group B (p < 0.0001) (Table 2).

Over the course of the study, Group A consistently exhibited a greater mean increase in serum vitamin D levels compared to Group B at all follow-up intervals. At three weeks, the mean increase in vitamin D levels was 3.15 ± 1.17 ng/mL in Group A, significantly higher than the 1.61 ± 0.28 ng/mL observed in Group B (p < 0.0001). At six weeks, Group A's mean increase rose to 10.82 ± 2.12 ng/mL, while Group B's mean increase was 7.83 ± 1.41 ng/mL (p < 0.0001). By twelve weeks, the mean increase reached 16.0 ± 2.99 ng/mL in Group A compared to 10.9 ± 3.17 ng/mL in Group B (p < 0.0001). These findings indicate a statistically significant greater improvement in vitamin D levels over time in Group A relative to Group B (Table 3).

Table 1. Comparison of Baseline Study Variables.

	Study Group		P-value
	Group A (N=110)	Group B (N=110)	
Age (Years)	6.52±1.95	6.54±1.97	0.93
Gender (%)			
Male	75 (57.7%)	74 (56.9%)	0.9
Female	55 (42.3%)	56 (43.1%)	
Baseline Lab Investigations			
Serum Calcium (mg/dL)	9.91±0.6	9.93±0.58	0.72
Serum Phosphate (mmol/L)	1.49±0.11	1.48±0.12	0.63
Alkaline Phosphatase (IU/L)	223.87±9.35	222.35±8.30	0.20
Serum Vitamin D Levels (ng/mL)	15.30±2.6	15.68±2.4	0.28

Table 2. Comparison of Lab Investigations at 12 Weeks Follow-up.

	Study Group		P-value
	Group A (N=110)	Group B (N=110)	
Serum Calcium (mg/dL)	11.29±1.23	11.23±1.21	0.71
Serum Phosphate (mmol/L)	1.63±0.19	1.61±0.18	0.43
Alkaline Phosphatase (IU/L)	247.86±6.36	247.28±6.29	0.49
Serum Vitamin D Levels (ng/mL)	31.3±1.48	26.6±1.81	<0.0001

Table 3. Comparison of Mean Increase in Vitamin D Levels over time between two Groups.

	Study Group	P-value

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	Group A (N=110)	Group B (N=110)	
Mean Increase in Vitamin D Levels at Three Weeks (ng/mL)	3.15±1.17	1.61±0.28	<0.0001
Mean Increase in Vitamin D Levels at Six Weeks (ng/mL)	10.82±2.12	7.83±1.41	<0.0001
Mean Increase in Vitamin D Levels at Twelve Weeks (ng/mL)	16.0±2.99	10.9±3.17	<0.0001

DISCUSSION:

Vitamin D is essential for maintaining the balance of calcium and phosphorus in the body, particularly in the processes that lead to bone mineralization and the development of bone mass. In addition to its well-known effects on the skeletal system, recent research has revealed that vitamin D also has important functions beyond the bones. These extraskeletal actions may influence the development of various health conditions, including infectious diseases and autoimmune disorders.[7]

Hypovitaminosis remains a widespread global concern. The incidence of vitamin D deficiency ranges from approximately 30% to 50% across various populations, impacting over one billion children and adults worldwide.[8, 9] Adults with insufficient vitamin D levels face numerous health issues, including musculoskeletal pain, fibromyalgia, osteopenia, osteoporosis, and it can lead to rickets in children. Rickets manifests in two forms: calcipenic and phosphopenic, with calcipenic rickets primarily caused by a lack of vitamin D.[10] Currently, there are two main methods for administering vitamin D to those deficient: oral and injectable forms of cholecalciferol. These treatments are used in both pediatric and adult patients. The choice of administration method typically depends on the pediatrician's clinical judgment and considerations of the patient's preferences and behavior.[10, 11]

In present study we found that oral therapy of vitamin D is more effective than IM therapy in increasing vit. D levels. In our study mean vitamin D levels were significantly high in oral therapy group in comparison to IM group; 31.3±1.48 ng/mL versus 26.6±1.81 ng/mL respectively. Mean increase in vitamin D levels from baseline at 12 weeks was also more in oral therapy group 16.0±2.99 ng/mL versus 10.9±3.17 ng/mL in IM group.

The present study results supports the findings of the study by Zabihiyeganeh et al. The authors reported that mean serum vitamin D level at twelve weeks was higher with oral stoss therapy (90 ± 11.2 nmol/L) versus intramuscular stoss therapy (58.8 ± 8.9 nmol/L).[12]

Contrary to our findings, Gupta and colleagues demonstrated that intramuscular (IM) therapy surpasses oral treatment in efficacy for patients with vitamin D deficiency. Their study on adults revealed that serum vitamin D levels measured at six and twelve weeks were 20.20 ± 1.65 ng/mL and 16.66 ± 1.36 ng/mL, respectively, with oral vitamin D administered via stoss therapy. In comparison, the levels with IM stoss therapy were 20.74 ± 1.81 ng/mL at six weeks and increased to 25.46 ± 1.37 ng/mL at twelve weeks, indicating that IM therapy resulted in a higher vitamin D level at twelve weeks but had comparable levels to oral therapy at six weeks. A significant confounding factor in this study was the baseline vitamin D levels, which were notably higher in patients assigned to IM therapy than in those receiving oral treatment.[6]

In the research conducted by Mondal and colleagues, the impact of a single intramuscular injection of 600,000 IU of vitamin D was contrasted with that of an oral vitamin D dose. The findings indicated no notable difference in effectiveness between the two methods when evaluated through biochemical and radiological assessments. Ultimately, the study concluded that both oral administration and a one-time intramuscular injection of 600,000 IU of vitamin D are safe and effective options for treating nutritional deficiencies.[13]

Wylon and colleagues conducted an in-depth investigation into the pharmacokinetics of a single intramuscular dose in comparison to prolonged oral vitamin D supplementation. Their findings indicated

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that, after 28 days, there was no statistically significant difference in serum 25 (OH) D levels between the two administration methods.[14]

In a previous study, both oral and intramuscular treatment methods led to significant increases in serum vitamin D levels. However, the increase from baseline after three months was notably greater in the group that received the oral treatment compared to the injectable form, with respective values of 90.0 ± 11.2 nmol/L and 58.8 ± 8.9 nmol/L (P = 0.03). The calculated standard deviations were 75.9 and 60.3 nmol/L.[15] Additionally, it was observed that both treatment methods were generally well tolerated; however, the injectable form demonstrated a statistically significant difference.[16]

The present study is limited by small sample size. Studies with very large sample sizes, involving multiple institutions should be conducted to determine either oral or IM vitamin D therapy is superior in treating vitamin D in children.

Conclusion:

Oral vitamin D is superior to intramuscular therapy in treating vitamin D deficiency in children.

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