ORIGINAL ARTICLE

Oral versus Intramuscular Route of Administration of Vitamin D Supplementation in Pediatric Population

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ABSTRACT

Background: Deficiency of vitamin d can lead to a number of serious long-term health problems. The current study determined the optimum route of vitamin D administration in children.

Methodology: This was a longitudinal study conducted at the Pediatrics Department, Liaquat University of medical and health sciences (LUMHS), Jamshoro. All children aged between 1 to 5 years were eligible to take part in the study. 2cc of the blood sample was extracted from the vein over the dorsum of the left hand and sent to the research laboratory for examining Vitamin D level. The vitamin D levels were measured at baselines, 4th month, and 12th month of treatment. After enrollment, children were divided equally into two groups, Group A and Group B. Group A received a dose of 600,000 U injection intramuscularly at 0, 4th, and 12 months and group B, received a dose of 600,000 U orally on 0, 4, and 12 months by ampoule. Serial vitamin D estimation was done at 0, 4, and 12 months. All data were collected on a pre-designed study proforma.

Results: It was found that both routes of vitamin D administration were equally effective. Patients who were administered vitamin D via intramuscular route had significant improvements by the fourth month as compared to the baseline levels (11.4 ± 3.4 vs 33.5 ± 6.7, $p<0.001$). Similarly, the mean baseline levels in patients who were administered the supplements orally were significantly increased by the fourth month ($p<0.001$). We found no correlation between different age groups and severity of deficiency at different intervals of time. The majority of the patients by the fourth month of treatment reached the peak range of vitamin D however, many reverted back to mild to moderate deficiency by the twelfth month. Upon assessing the adverse effects of the two routes, it was found that the oral route was significantly associated with increased rates of vomiting as compared to the intramuscular route [16 (20.51%) vs 8 (10.26%), $p<0.001$].

Conclusion: We revealed that both oral and intramuscular routes of administration of vitamin D were efficacious and successfully attained peaks by the fourth month of treatment. Only a few children experienced vomiting, pain on site of injection, and abdominal pain after receiving their dose of medication. It is recommended that the intramuscular route should be preferred in cases where children are suspected of malabsorption.

Keywords: Hypovitaminosis, Children, Vitamin D, Vitamin D deficiency, Vitamin D supplementation, Route

INTRODUCTION

Vitamin D in the B ring of the cyclopentanoperhydrophenanthren structure is a secosteroid with incomplete 9, 10 carbon-carbon bond. The most potent or less potent cholecalciferol(D2) is classified as vitamin D and its metabolites. The steroid nuclear receptor Vitamin D receptor (VDR) has been supposed to be active in vitamin D [1-2]. The region consists of three regions: the C-site and the hinge region binding with two zincs, which binds deeply at individual points. Vitamin D-specific receptor areas and their different genes vary from cell to cell with some, though not overlapping, especially when vitamin D is exposed to various cells[3]. In deficiency states, Vitamin D mobilizes calcium in the bone. It is mainly necessary for bone and muscle maintenance. Deficiency of vitamin D decreases VDR differentiation and surreglation of osteoblasts in mature osteoblasts, leading to increased bone loss and osteoclastogenesis suppression by osteoblast [4]. Vitamin D promotes parathyroid gland reaction to calcium by initiating its receptor gene development in some promoters at two receptors [5]. The risk of myocardial infarction is increased if vitamin D is reduced. Diet contains a small amount of vitamin D like oily fish and eggs (20-50 units per egg), margarine, cereals for breakfast, milk formula, and vitamin D fortification in breast milk [6]. Previous studies indicate the connection between obesity and the 25-hydroxyvitamin D level of lower serum [7]. There are evidence. Vitamin D deficiency is considered to be less than 20 ng/mL in the pediatric population by the American Academy of Pediatrics and others [8]. Vitamin D deficit is considered to be less than 15 ng/mL in one base. A study in Melbourne found that 98% of children had ricket and 81% of mothers had vitamin D levels that are consistent with osteomalacia in women without vitamin D supplementation [9]. A study was carried out by Khattak AA, which reported that 66% of children under the age of one years had active rickets and 18% of 1 to 2 years old [10]. The prevalence of vitamin D deficiency among children in Pakistan is 41%[11].

MATERIALS AND METHODS

This was a longitudinal study conducted at the Pediatrics Department, Liaquat University of medical and health sciences (LUMHS), Jamshoro after obtaining approval from the ethical board committee. All children aged between 1 to 5 years were eligible to take part in the study. Children already on vitamin D supplementation, or those diagnosed with rickets or hypoparathyroidism, or a bleeding disorder were excluded from the study. A non-probability convenience sampling technique was applied to recruit children in the study. Informed verbal and written consent of participation was taken from each child's parents prior to the enrollment. The sample size for the study was obtained by taking the prevalence of vitamin D deficiency in children from 1 to 5 years as 41%, risk prevalence ratio of 1.6, risk prevalence difference of 23 with 95% confidence level and 5% margin of error. A total sample size of 156 was obtained.

2cc of the blood sample is taken from the vein via the left-hand dorsum and transmitted to the research laboratory in determining the vitamin D deficiency. The vitamin D levels were measured at baselines, 4th month, and 12th month of treatment. For one year, the children were followed. Visits were frequent for 0, fourth month and 12 months. The children were divided into two groups, Group A and Group B, equally following enrollment. Group A received a dose of 600,000 U injection intramuscularly at 0, 4th, and 12 months and group B, received a dose of 600,000 U orally on 0, 4, and 12 months by ampoule. Serial vitamin D estimation was done at 0, 4, and 12 months. After reports within 24 hours, the blood samples were discarded and were not used for further studies. During each visit, all patients were assessed for side effects of vitamin D supplementation either by oral or intramuscular injection like pain, abdominal pain, vomiting, and swelling over the injection site. All data were collected on a pre-designed study proforma. The researchers have recorded socio-demographic and clinical parameters.

Data were analyzed using the statistical software "Statistical Package for Social Sciences, SPSS version 22.0". All categorical variables like gender, complications, and outcome were presented as frequency and percentage. The relationship between different age groups and vitamin deficiency at different intervals was assessed using Chi-Square Tests and Fischer's exact test. Repeated Measure ANOVA and Paired Sample t-test was applied to determine the optimum route of administration (oral vs intramuscular). A p-value of < 0.05 was set as statistically significant.

RESULTS

A total of 156 cases fulfilling the inclusion/exclusion criteria were enrolled to determine the frequency of Vitamin D deficiency in children between 1-5 years who attended the OPD of Liaquat University Hospital, Hyderabad. Sixteen patients were lost follow-up and considered dropped from the study. Age distribution of the patients was done, 40 (25.6%) were between one-two years of age while 74 (47.4%) were between three-four years of age, 42 patients 27% more than four years. Gender distribution shows that 95 (60.8%) were male and 61 (39.1%) were females. The residential status of the patients was recorded which shows that 90 (57.6%) were urban and 66 (30%) belonged to the rural areas. The frequency of dropouts from both groups was 10 (6.4%) in group A while 6 (3.4%) from group 2. The mean weight was 5.32±7.8 kgs. Mean vitamin D levels were 16.3±7.3 ng/mL.

It was found that both routes of vitamin D administration were equally effective (table 1). Patients who were administered vitamin D via intramuscular route had significant improvements by the fourth month as compared to the baseline levels (11.4 ± 3.4 vs 33.5 ± 6.7, $p<0.001$). Similarly, the mean baseline levels in patients who were administered the supplements orally were significantly increased by the fourth month ($p<0.001$).

Table 1: Mean levels of Vitamin D at Baseline, 4-months, and 12-months of Treatment
a = Repeated Measure ANOVA
b = Paired Sample t-test

Groups	Baseline	4 months	12 months	P-value
Intramuscular	11.4 ± 3.4	33.5 ± 6.7	18.2 ± 6.4	<0.001[a]
Oral	9.3 ± 7.8	34.1 ± 7.4	19.7 ± 7.5	<0.001[a]
P-value	0.963[b]	0.596[b]	0.181[b]	

Table 2 portrays the relationship between varying degrees of deficiencies and the effect of different age groups at different time intervals of the study. We found no correlation between different age groups and severity of deficiency at different intervals of time. The majority of the patients by the fourth month of treatment reached the peak range of vitamin D however, many reverted back to mild to moderate deficiency by the twelfth month.

Table 2: The Relationship Between Severity of Deficiency and Age at Different Time Intervals of the Treatment
c= Chi-square test
f= Fischer's exact test

Age Group	Mild Deficiency (21-30 ng/dl)	Moderate Deficiency (10-20 ng/dl)	Severe Deficiency (<10 ng/dl)
At Baseline			
1-2 (n=40)	6 (15.00%)	21 (52.50%)	13 (32.50%)
3-4 (n=74)	16 (21.62%)	36 (48.65%)	22 (29.73%)
>4 (n=42)	10 (23.81%)	17 (40.48%)	15 (35.71%)

0.767[c]			
At 4th month			
	Normal (>30 ng/dl)	Mild Deficiency (21-30 ng/dl)	Moderate Deficiency (10-20 ng/dl)
1-2 (n=40)	37 (92.50%)	2 (5.00%)	1 (2.50%)
3-4 (n=74)	68 (91.89%)	5 (6.76%)	1 (1.35%)
>4 (n=42)	38 (90.48%)	3 (7.14%)	1 (2.38%)
0.980[f]			
At 12th month			
	Normal (>30 ng/dl)	Mild Deficiency (21-30 ng/dl)	Moderate Deficiency (10-20 ng/dl)
1-2 (n=40)	13 (32.50%)	21 (52.50%)	6 (15.00%)
3-4 (n=74)	23 (31.08%)	40 (54.05%)	11 (14.86%)
>4 (n=42)	13 (30.95%)	23 (54.76%)	6 (14.29%)
P = 0.999[c]			

Upon assessing the adverse effects of the two routes, it was found that the oral route was significantly associated with increased rates of vomiting as compared to the intramuscular route [16 (20.51%) vs 8 (10.26%), p<0.001] (Table 3).

Table 3: The Adverse Effects Of Vitamin D Supplements in Patients (Intramuscular vs Oral) (N=156)
f= Fischer's exact test

Groups	Pain/Swelling	Vomiting	Abdominal Pain	P-value
Intramuscular	19 (24.36%)	8 (10.26%)	8 (10.26%)	<0.001[f]
Oral		16 (20.51%)	8 (10.26%)	

DISCUSSION

Vitamin D deficiency is prevalent all over the world, especially in the developing world. There are few studies on the subject of vitamin D deficiency in children [12-15]. A study from Lahore revealed that the majority of the rickets patients were male [13]. Similar demographics were reported in another study by Mazari et al [14]. We reported a mean vitamin D level of 16.3±7.3 ng/mL. Our study did not reveal any significant relationship between gender and vitamin D deficiency, which was similar to a study by Karnavat [15]. In our study, we divided the children into two groups, oral and intramuscular, and followed for one year. We reported peak levels of vitamin D in both groups by the 4th month of treatment which reduced to <20 ng/mL by the 12th month of treatment Similar patterns of vitamin D levels were revealed in a study from Iran. Researchers randomized 92 patients in two groups with vitamin D deficiency less than 30 ng/mL. Vitamin D blood levels were measured at baseline, three, and six months of treatment with vitamin D supplementation with oral versus intramuscular routes [16]. The researchers found that both treatments caused significantly raised vitamin D levels. Vitamin D status at three months was significantly better in the oral group than in the intramuscular injection group (p=0.03). At 6 months, levels of both groups were similar i.e. 20.8 and 24.8 ng/mL, respectively [16]. In our study, both groups have shown a steady increase in vitamin D for 6 months. Previous studies have preferred oral formulations for nutritional causes and intramuscular preparations are preferred in cases with underlying malabsorption [17]. A research has shown 100 percent compliance, but unforeseen bioavailability, slower starting replication and additional administrative burden have resulted. The intramuscular administration. Thus, the first-line treatment solution is oral replacement. The mega dose of 600,000 IU is compared intramuscularly with the oral dose of Cipriani C et al. It has shown that the oral doses have better initial outcomes than intramuscular vitamin D, however over the next 4 months, the intramuscular dose has produced a steady increase in continuous levels [18]. We found that both routes of administration attained peaks at the fourth month of the administration and then gradually decreased to a normal level by the twelfth month of the treatment. These findings are in accordance with the previous literature [19]. After intramuscular injection, vitamin D levels were increased in all subjects and after 3 months of the injection, decreased to less than 20ng/ml in 87.5% of patients [20]. We conclude that both oral and intramuscular routes of administration are efficacious in attaining peak levels of vitamin D in patients with hypovitaminosis.

CONCLUSION

Vitamin D deficiency is very common in our setting. We revealed that both oral and intramuscular routes of administration of vitamin D were efficacious and successfully attained peaks by the fourth month of treatment. Only a few children experienced vomiting, pain on site of injection, and abdominal pain after receiving their dose of medication. It is recommended that the intramuscular route should be preferred in cases where children are suspected of malabsorption. Further large-scale studies should be conducted to ascertain these findings and explore the long-term efficacy of these different routes.

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