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Efficacy of Parenteral versus Oral Vitamin D Replacement in Hypovitaminosis D.

Rizwan Rasul Khan[1], Salman Azhar[2], Huma Rasheed[3], Muhammad Rizwan[4], Muhammad Sarfraz[5], Hassan Akhtar Bukhari[6]

1. MBBS, FCPS (Med)
Associate Professor of Medicine
Aziz Fatimah Medical & Dental College, Faisalabad.
2. MBBS, FCPS (Med)
Assistant Professor of Medicine
The University of Faisalabad.
3. PhD.
Assistant of Professor
Institute of Pharmaceutical Sciences,
University of Veterinary and Animal Sciences, Lahore.
4. MBBS, MCPS (Family Medicine), FCPS (Med)
Assistant Professor Medicine
Aziz Fatimah Medical and Dental College, Faisalabad.
5. MBBS, FCPS (Med)
Associate Professor of Medicine
Independent Medical College, Faisalabad.
6. MBBS, FCPS (Med)
Assistant Professor of Medicine
The University of Faisalabad.

Correspondence Address:
Dr. Rizwan Rasul Khan
Department of Medicine
Aziz Fatimah Medical & Dental College, Faisalabad.
drrizwan218@yahoo.com

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ABSTRACT… The study was to compare efficacy of parenteral versus oral vitamin D replacement in hypovitaminosis. **Study Design:** Randomized trial. **Setting:** Medical Outpatient Clinics of Madinah Teaching Hospital, Chiniot General Hospital and Maqsooda Zia Hospital, Faisalabad. **Period:** 6 months (Oct 2017 – Apr 2018). **Material & Methods:** 84 patients were included in the study. Baseline 25(OH) D levels were determined, and followed-up at 3rd and 6th weeks following vitamin D replacement. After giving the first dose of vitamin D (parenteral or oral), patients were given maintenance dose of calcium and vitamin D supplement as per recommended daily allowance (RDA). Patients with significant clinical improvement were also noted in both groups. **Results:** The change in vitamin D level after 3 weeks and 6 weeks of replacement through oral route and intramuscular (IM) route was compared; which was found to be statistically significant in both groups (p value < 0.05). Mean change in vitamin D levels after 6 weeks of replacement in all the patients was 17.96 + 13.0. In oral group, it was 13.5 + 10.07 and in IM group, it was 22.40 + 14.18. This clearly shows that it was higher in the IM group compared to the oral group. This difference was statistically significant ($p=0.001$). The percentage change in the serum 25-OH D level was 53% and 79% for oral group compared to 103% and 207% for the IM group, y after 3 and 6 weeks of replacement respectively. **Conclusion:** While managing hypovitaminosis D, IM route of administration is more effective. There was significant improvement in the serum 25OHD levels in the IM group. A larger randomized control trial should be done comparing the efficacy of oral and IM route of vitamin D replacement.

Key words: Hypovitaminosis D, Oral Vitamin D, Parenteral Vitamin D, Vitamin D Replacement.

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INTRODUCTION

Among the organic substances in the human body, vitamins play a major role in different metabolic pathways. Unfortunately, these vitamins are deficient in the general population in developing as well as developed countries. As far as vitamin D is concerned, even in the absence of any malabsorption, it is deficient among the individuals who are not exposed to sunlight for one reason or the other.[1] Furthermore, only a few naturally occurring food products contain vitamin D and poor skin conversion makes the deficient pool even larger.[2]

The natural form of vitamin D is cholecalciferol or vitamin D_3 and 70% of it is formed in the skin by the action of ultra-violet (UV) light on 7-dehydrocholesterol, a metabolite of cholesterol and the remaining 30% comes from diet. Vitamin D is converted in the liver to 25-hydroxy vitamin D (25(OH) D), which is further hydroxylated in the kidneys to 1, 25-dihydroxy-vitamin D (1, 25 $(OH)_2 D$), the active form of the vitamin. 1, 25$(OH)_2$ D activates specific intracellular receptors which influence calcium metabolism, bone mineralization and tissue differentiation. There is increasing evidence that vitamin D is important for immune and muscle function.[3]

Thus, the deficiency of vitamin D in both children and adults have a broad spectrum of manifestations ranging from fatigue, myalgias, bone pains, proximal muscle weakness, fragility fracture, osteomalacia, etc.[3]

Riaz H et al. reported that among the Pakistani population, prevalence of vitamin D deficiency is 53.5% and insufficient levels in 31.2%.[4] In another study, it was concluded that 92% of the population to be suffering from hypovitaminosis D.[5] Thus, in a society with such a huge scale of deficiency of such an important vitamin, an effective methodology should be in place to manage human misery.

Vitamin D replacement strategies vary among physicians. Oral as well as parenteral preparations are available and mix opinion prevails in different work groups in replacing vitamin D. Due to the paucity of evidence regarding best route (parenteral v/s oral) to replace vitamin D, we conducted this study in Faisalabad among the adult population, not suffering from any other co-morbidity, yet complaining of non-specific symptoms of fatigue, myalgias, cramps, muscle stiffness, etc. Aim was to compare the efficacy of intramuscular route with oral route for vitamin D replacement as many patients taking vitamin D injections orally did not seem to benefit much. So present study was conducted to compare the common practice of taking vitamin D injection orally with the one of injecting the same preparation intramuscularly. The route with better efficacy should be recommended in severely deficient patients.

MATERIAL & METHODS

In this randomized trial, 84 patients meeting the inclusion and exclusion criteria in the medical outpatient clinics of Madinah Teaching Hospital, Chiniot General Hospital and Maqsooda Zia Hospital, Faisalabad were included in the study during 6 months (Oct 2017 – Apr 2018). An inclusion criterion was 'All patients of age 12 to 70 years meeting the operational definition of hypovitaminosis D.'

The objective of this study was to compare the efficacy of parenteral (IM) with oral vitamin D replacement in otherwise healthy patients with hypovitaminosis D. Hypovitaminosis D was defined as any patient having serum 25-(OH) D levels less than 30ng/ml. Patients with more than 50% improvement of 25-OH-D level after 6 weeks of replacement were labeled as having significant improvement. Patients suffering from any organic or psychiatric illness apparent clinically were also excluded from the study. All patients were also screened beforehand for anemia, diabetes mellitus, chronic hepatitis B & C, early chronic kidney disease, hypothyroidism, and hyperuricemia, the conditions which may not be diagnosed clinically.

Informed consent was obtained at the start of the study. Demographic data like name, age, gender, address and contact numbers were noted. Patients were randomized using the same injectable brand and were labeled as I/M group and oral by consecutive non-probability sampling technique. The baseline 25(OH) D levels were determined and then first dose of vitamin D administered. 2nd 25 (OH) D levels were then measured after three weeks and second dose was administered. Third level then measured after another three weeks of second dose. Serum 25(OH) D levels carried out on Advia Centaur instrument employing chemiluminescent micro particle immunoassay (CMIA) from Agha Khan Laboratories, Karachi. After giving the first dose of vitamin D (parenteral or oral), patients were given maintenance dose of calcium and vitamin D supplement as per RDA. Patients with significant improvement were also noted in both groups.

All data was collected on the predesigned proforma. Statistical analysis was carried out using SPSS version 20. Frequency and percentage was calculated for all the qualitative variables including gender. Mean with standard deviation was calculated after analysis of continuous data including vitamin D level at baseline, after 3 weeks and after 6 weeks and mean change in the serum 25 –OH- vitamin D from baseline till 6 weeks was recorded. The mean change in vitamin D level after 6 weeks of replacement was compared in the two groups using t-test and percentage of patients with significant change in the vitamin D level was compared using Chi-square test; considering p value < 0.05 to be significant.

RESULTS

In this randomized controlled trial, out of 84

patients included, 11 were males and 73 were females. The mean age of patients was 35.17 + 10.05 years, with minimum age being 19.0 and maximum was 54 years. 31 out of 84 patients belonged to age less than 30 years while 13 of 84 were of age more than 45 years. Rest of the patients were between 30 to 45 years of age.

They were randomly divided into two groups. In IM group, 3 of 42 cases were male and rest 39 were females while in the oral group, 8 of 42 cases were male and rest 34 were females.

Vitamin D (25-OH-D) level was seen at the baseline, after 3 weeks and 6 weeks. All the quantitative variable of the oral and IM group is shown in the Table-I and Table-II.

The change in vitamin D level after 3 weeks and 6 weeks of replacement through oral route and intramuscular route was compared within the same group; and was found statistically significant in both groups (p value < 0.05). Mean of change in vitamin D level after 6 weeks of supplements in all the patients was 17.96 + 13.0. In oral group, it was 13.5 + 10.07 and in IM group, it was 22.40 + 14.18. This clearly showed statistically significant higher trend in IM group (p=0.001).

The overall percentage change in the serum 25-OH D level was 77% after 3 weeks and 141% at 6 weeks in our study. This was 53% and 79% for oral group compared to 103% and 207% for the IM group, respectively after 3 and 6 weeks of replacement.

On vitamin D replacement through oral or IM route, 35 of 84 (41.7%) patients with vitamin D deficiency showed significant improvement in terms of clinical well-being, 23 (65.7%) were of IM group and 12 (34.2%) were of oral group; this difference was statistically significant also (p value = 0.01).

Patients with significant clinical improvement were mostly of age less than 30 years. None of the patients of age above 45 years showed such significant improvement.

Variable	N	Minimum	Maximum	Mean	Std. Deviation
D levels before	42	9.31	59.20	25.0148	12.98583
D levels after 3 weeks	42	17.40	73.60	34.2095	12.31766
D levels after 6 weeks	42	22.90	68.40	38.5381	12.08436
Age (years)	42	22.0	52.0	36.952	8.0697

Table-I. Showing the quantitative data of oral supplementation group

Variable	N	Minimum	Maximum	Mean	Std. Deviation
D levels at baseline (ng/mL)	42	4.20	54.60	21.3424	12.66141
D levels after 3 weeks (ng/mL)	42	23.70	48.60	31.6405	8.10267
D levels after 6 weeks (ng/mL)	42	31.00	64.10	43.7476	9.23612
Age (year)	42	19.0	54.0	33.381	11.5102

Table-II. Showing the quantitative data of IM supplementation group

Significant change in Vitamin-D (50% or more)			
Age groups (years)	**No**	**Yes**	**Total**
less than 30	12	19	31
31 to 45	24	16	40
46 and above	13	0	13
Total	49	35	84

Table-III (A). Showing significant reduction in vitamin D level in relation to age

Group		Baseline	After 3 weeks	After 6 weeks
Oral	Mean	25.0148	34.2095	38.5381
	SD	12.98583	12.31766	12.08436
IM	Mean	21.3424	31.6405	43.7476
	SD	12.66141	8.10267	9.23612
P-value		0.781	0.439	0.712

Table-III (B). Serum vitamin D levels (ng/ml) in patients included in the group

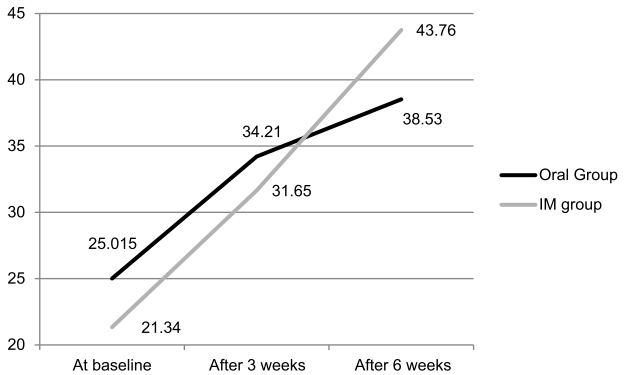

Figure-1. Showing the change in 25-OH D level in ng/ml (taken on vertical axis) after oral vs IM vitamin D therapy

DISCUSSION

Hypo-vitaminosis D or vitamin D3 deficiency is a global health issue.[1] Over the counter replacement is inadequate for its prevention and mostly higher doses are required for its management.[2] Various dosing protocols are used for vitamin D replacement, but very limited data about local guidelines are available. We designed our study to compare the efficacy in terms of mean change and significant improvement in serum 25-OH-D level after 6 weeks of intramuscular and oral vitamin D replacement in cases of hypo-vitaminosis-D.

Gupta N et al, in a similar study, reported mean 25OHD serum level at the start to be 5.9 ± 1.1 ng/mL and 7.4 ± 1.15 ng/mL (P=0.33) in oral group and IM group, respectively. Patient population selected was apparently healthy (resident doctors, nursing staff). After six weeks of oral vitamin D replacement, the level increased to 20.2 ±1.7 ng/mL at 6 weeks and 16.7 ±1.4 ng/mL at 12th weeks of replacement. In IM group, the levels were 20.7±1.8 ng/mL and 25.5±1.4 ng/mL after 6 & 12 weeks of replacement respectively. The reason for a fall in vitamin D levels at 12th week among oral vitamin D group was a lack of supplementation or a lack of maintenance dose as elaborated by Whyte et al.[6] However, this phenomenon of a fall in vitamin D levels was not observed in the IM group indicative of a sustained response with IM group and clearly outweighing the oral group. This clearly shows that, after 12 weeks of vitamin D replacement, mean serum vit-D25OHD level was better and improved in the IM supplement group of population compared to oral route of replacement (P<0.001).[7] These results show similar trends as those of our study. In our study we did replace according to the recommended daily allowance (RDA), so a sustained rise was observed.

In contrast to this study, Shahrivari M, et al. reported different results.[8] He studied 84 patients of vitamin D deficiency and insufficiency into two replacement protocols as weekly oral vitamin D replacement 50,000IU for one month followed by monthly dose for next 2 months for vitamin D insufficiency patients; whereas, oral vitamin D 50,000IU weekly for two months and then monthly for one month for vitamin D deficient patients. In both the groups, IM replacement of vitamin D 3,00,000IU was once monthly for 3 months. Baseline levels were almost same but serum levels after replacement through two different routes of treatment was higher in oral group compared to injection group. (P=0.023). After 3 months about 76% of oral group achieve the sufficient cutoff level compared to about 57% patients in the IM group (P=0.064). This was also against the results of our study. He also reported that oral route of treatment had a better percentage change in overweight patients (P=0.046). Relation of improvement in vitamin D level with BMI was not studied in our study.

Zabihiyeganeh M, et al. studied 92 patients with serum 25 (OH) D deficiencies after dividing them into oral and parenteral group.[9] Increase or change in the serum 25 (OH) D measured at the start of the study and later after 3 & 6 months was compared. Both treatment regimens significantly increased the serum 25 (OH) D levels. Although increase was noted in both the groups, but mean change till 3 months was significant and higher in the oral group than in IM group (P=0·03). On the contrary, the change was almost the same after 6th months; but more percentage of people in the oral group achieved the adequate level of vitamin D. They concluded that both the regimens were effective and safe, but oral route showed early response. These results were opposite to the findings noted in our study.

Another study by Kumari N, et al favored IM route of administration of cholecalciferol in women with vitamin D deficiency.[10] 100 female patients were followed till 12 months and serum 25(OH) D levels, serum calcium level and bone density was compared from baseline till 12 months. All patients were advised replacement of vitamin D through oral or intramuscular route with daily calcium (1000 mg) orally. Bone density was seen and compared at the neck of femur and lumber spine, on 3 monthly follow-up. Calcium and vit-D was compared 3 monthly and bone density at 6 & 12 months. Both treatment groups showed response to supplements, the IM route showed better and sustained results (85.7% versus 22.9%). Bone density was not improved significantly in both groups. Bone density was not compared in our study.

Study by Terrence et al on the use of IM vitamin D preparation, revealed a 128% rise in the baseline vitamin D levels after a follow up of 12 months.[11] This study enrolled patients with vitamin D deficiency, with a large female population as compared with the male participants. They used high dose of vitamin D i.e. 6,00,000IU (15mg) IM one stat dose. After a follow up of 1 year, there was statistically significant improvement in vitamin D levels of the participants (P<0.001).

In pediatric population, IM supplementation has better outcome as shown by Billoo AG et al.[12]

LIMITATION OF THE STUDY

Our study was limited due to the shorter follow up period. We suggest a larger sample size, long follow up, including other variables like BMI and assessing bone density in the follow up would further consolidate the decision regarding adequate replacement regimen.

CONCLUSION

While managing hypovitaminosis D, IM route of administration is more effective. There was significant improvement in the serum 25OHD levels in the IM group. A larger randomized control trial should be done comparing the efficacy of oral and IM route of vitamin D replacement.

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CONFLICTS OF INTERESTS

The authors declare that they have no conflicts of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Rizwan Rasul Khan	Data collection, Analysis.	
2	Salman Azhar	Data collection, Analysis, Paper writing.	
3	Huma Rasheed	Paper writing.	
4	Muhammad Rizwan	Data collection	
5	Muhammad Sarfraz	Data collection	
6	Hassan Akhtar Bukhari	Data collection