ORIGINAL ARTICLE

Comparing Different Routes of Vitamin D Administration: A Randomized Interventional Trial

Jamal Ara[1], Saleem Aminullah Paracha[1], Nooruddin Sadaruddin[2], Farah Asad[3], Amna Begum[4], Aneela Altaf Kidwai[1]

[1]Department of Medicine, Karachi Medical and Dental College and Abbasi Shaheed Hospital, Karachi, [2]Orthopedic Surgery Department, Imam Clinic Hospital, Karachi, [3]Department of Pharmacology, Sindh Medical College, Jinnah Sindh Medical University, Karachi, [4]Department of Gynecology, Karachi Medical and Dental College and Abbasi Shaheed Hospital, Karachi, Pakistan.

ABSTRACT

Background: Vitamin D maintains overall good health by boosting up of the immune system through proper function of lungs, heart, muscles, brain and bones. The goal of the study was to determine and compare different routes and formulation of vitamin D3 that was per oral, injectable formulation given orally and intramuscular injection in patients of different groups.

Methods: This was a randomized clinical trial designed for vitamin D deficient patients. Patients were randomly assigned to three routes of administration i.e. orally, injection formulation given orally andintramuscular injection group. For mild deficiency, 2 doses of 200,000 IU, for moderate deficiency, 3 doses of 200,000 IU and for severe deficiency, 4 doses of 200,000 IU, 25[OH] D was prescribed. Chi-Square (χ^2) test was used to evaluate the significant association .

Results: A total of 150 patients were enrolled in the study. The mean age ±SD of patients was 48.29 ± 4.65 years. At 4 and 12 weeks after completion of vitamin D3 replacement, levels of 25-hydroxycholecalciferol were measured. In the majority of participants of all three groups, the levels of vitamin D were increased to normal range by week 4 after the final dose of vitamin D3. However, the majority of patients failed to maintain their Vitamin D3 levels within the normal range 12 weeks after the final dose. All three routes of administration of Vitamin D were found equally effective with no significant difference between the routes (p>0.05).

Conclusion: All three routes of administration of vitamin D supplements had equal efficacy with no significant advantage over one another.

Keywords: Vitamin D3; Ergocalciferol; Cholecalciferol; 25-Hydroxycholecalciferol; Intramuscular; Oral; Rickets; Osteomalacia.

Corresponding Author:
Dr. Jamal Ara
Department of Medicine,
Karachi Medical and Dental College and Abbasi Shaheed Hospital,
Karachi, Pakistan.
Email: jamalarafasih@gmail.com
doi.org/10.36283/PJMD9-1/005

INTRODUCTION

Vitamin D is a group of fat-soluble vitamins that are either produced endogenously in the skin or absorbed from the diet. The two most important compounds of this group are Ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3). The synthesis of the endogenous vitamin D3 depends on the ultraviolet rays from the sun, which when in contact with the skin, trigger vitamin D synthesis in the body. For most individuals around 90% of the vitamin D is produced in this way, while remaining is obtained from the diet[1,2].

Vitamin D is essential for the human body; some of the important functions, which require vitamin D, are calcium absorption from the gut, regulation of serum calcium and phosphate concentration and maintaining adequate mineralization of bone. Deficiency of vitamin D in body can be associated with hypocalcemic tetany, rickets in children, and osteomalacia in adults. In a number of studies vitamin D has been implicated as an important factor in the pathogenesis of several neuromuscular disorders like dementia, autism, schizophrenia,

depression, multiple sclerosis, etc [3,4] . Vitamin D3 has an important role in neurodevelopment, immunological modulation, brain homeostasis, aging and gene regulation .

Medical practitioners have invested a lot of energy in evaluating various aspects of vitamin D deficiency (VDD). Several studies have highlighted the high prevalence of vitamin D deficiency globally[4,5]. However, the incidence of vitamin D deficiency is still indeterminate and data from other regions is ambiguous[6].

Local data regarding the frequency ofpatients suffering from vitamin D deficiency in Karachi (Pakistan) is considerably high. A recent study in Karachi revealed 62% patients were severely deficient in vitamin D[7]. In one of the studies conducted at Aga Khan University Hospital on healthy volunteers, a low serum 25-hydroxycholecalciferol (25[OH]D) in 94.3% of the females and 88.6% of the males was reported[8].

It is highly important to figure out the most efficient mode of compensating vitamin D deficiency in deficient individuals. Various regimens are being followed for vitamin D replacement with no clear guidelines. A study carried out at AKUH aimed at ascertaining the prevalence of vitamin D deficiency with oral and intramuscular administration of two high-dose preparations of vitamin D3. The study reported that 70% of the study participants were recovered from the deficiency of Vitamin D with a single dose of either 600,000 or 200,000 IU given orally or intramuscularly[9].

In order to assess the most effective regimen to overcome vitamin D deficiency in adults we need to ascertain not only the doses, but also the most appropriate route of vitamin D administration. Evaluating which form of vitamin D prescribed to vitamin D deficient patients was most effective in improving their levels will help patients in efficient and prompt recovery from symptoms and helped us to evaluate the difference in the results of the three modes of vitamin D administration. In addition to this, we had also extended our study to evaluate the frequency of patients developing VDD, 3 months after the replacement therapy.

METHODS

This randomized clinical trial was conducted in General Medical and Orthopedic outpatient clinic of Imam Clinic Hospital, Karachi, Pakistan, between October 2018 and March 2019. Patients who presented with myalgias, bone pains and joint pains were evaluated for vitamin D3 deficiency; those with vitamin deficiency and willing to participate were included in the study. The patients were classified into three categories of mild, moderate, and severe deficiency of Vitamin D. Patients with vitamin D levels between 21-30 ng/dl were grouped as mildly deficient, those between 10-20 ng/dl were defined as moderately deficient, while those with levels of <10 ng/dl were defined as severely deficient. They were randomly divided into three groups according to the formulation and routes of administration of Vitamin D i.e. Oral, Injection formulation given orally, and Intramuscular injection. Efficacy of the response was measured by vitamin D levels at 1 month and 3 months after final dose.

Dose regimes of same brand were specifically designed according to the level of deficiency. For cases of mild deficiency, 2 doses of 200,000 IU, 3 weeks apart were given. For cases of moderate deficiency, 3 doses of 200,000 IU on Day 0, Day 7, and Day 21 of diagnosis was given. Similarly, for the cases of severe deficiency, 4 doses of 200,000 IU, each one week apart was given.

All patients with chronic renal failure, chronic liver disease, known malignancy and pregnancy were excluded. In addition, patients who had received any form of vitamin D supplementation in the last three months were excluded. Informed consent from each participant was obtained prior to commencement of the intervention. The Institutional Ethical Review Board, Imam Clinic Hospital, approved the study.

A total of 300 patients were assessed initially for eligibility, out of which 150 patients were randomly assigned to each route of administration i.e. oral (group 1), Injection formulation given orally (group 2) and Intramuscular injection (group 3) intervention by using block randomization method. Those who were randomized to receive Intramuscular injection were given deep intragluteal injection.

The physician on site for all three groups, resulting in 100% compliance, administered the first dose. Patients were given dates for subsequent doses according to protocol. The patients were set up for a follow-up appointment for 1 and 3 months after the final dose of drug. Anthropometric parameters such as weight, height, age and BMI were recorded for the patients at each visit. The main outcome assessed was the delta change in mean serum 25-hydroxycholecalciferol level and achievement of serum 25-hydroxycholecalciferol ≥ 30 ng/dl at one and three months' post diagnosis.

Serum Vitamin D levels were measured by experienced laboratory technicians of National Institute of Blood Disease (NIBD) laboratory at baseline, at one and three months after the final dose of vitamin D3 was administered. Serum 25 Hydroxy Vitamin-D was determined by radioimmunoassay according to the standard instructions.

Data analysis was done using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). All continuous variables

were presented using mean and standard deviation (SD). Chi-Square (χ^2) test was used to evaluate the significant association between vitamin D levels and different routes of administration after one and three months. For the assessment of mean serum 25-Hydroxy Vitamin-D levels within each group, at baseline and last measurement, paired t-test was used. $p<0.05$ was considered statistically significant.

RESULTS

Initially, 50 participants in each of the three treatment groups i.e. oral treatment group (group 1), Injection formulation given orally treatment (group 2), and Intramuscular injection treatment (group 3) were assigned randomly.

In oral group treatment, 2 patients were lost to follow-up by week 12, while remaining 48 (96%) completed the treatment. In Injection formulation given orally group, 4 patients were lost to follow-up while 46 (92%) completed the treatment. In Intramuscular injection group, 4 patients were lost to follow-up while 46 (92%) completed the treatment (Figure 1).

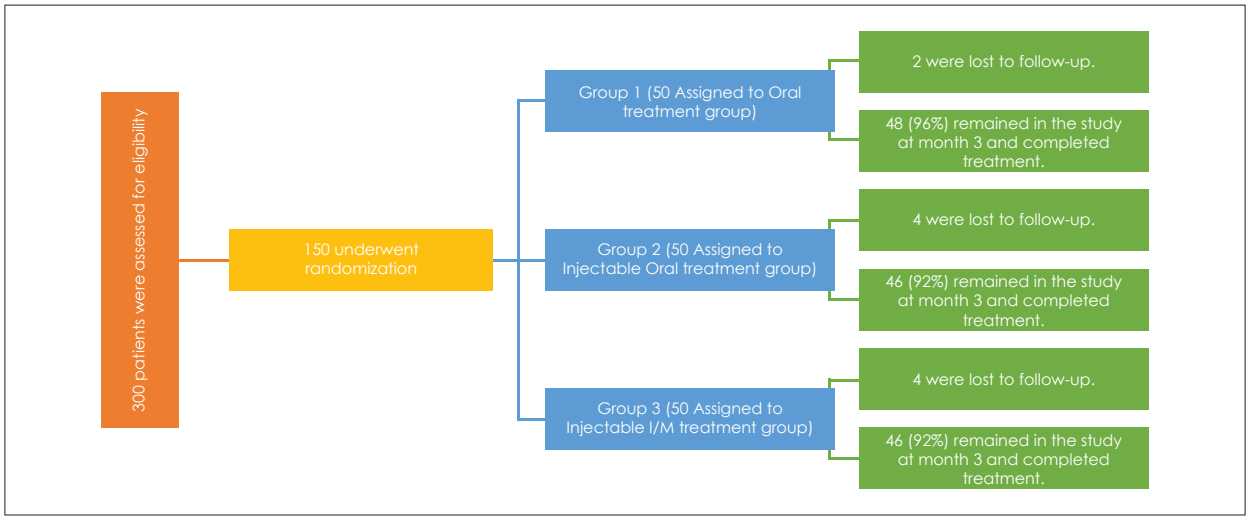

Figure 1: Flow diagram of enrolment, randomization and follow-up.

A total of 140 patients completed the course of the treatment. Out of these, 113 (80.7%) were female and 27 (19.3%) were male patients with mean age +SD was 48.29 +14.65 years. According to the baseline Vitamin D3 levels, 30 (21.4%) were mildly deficient (21-30 ng/dl), 61 (43.5%) were moderately deficient (10-20 ng/dl), while 49 (35%) were severely deficient (<10 ng/dl) in 25-hydroxycholecalciferol.

At diagnosis, 26 (23.0%) female and 4 (14.8%) male patients had mild deficiency, 47(41.6%) female and 14 (51.9%) male patients had moderate deficiency while 40 (35.4%) female and 9 (33.3%) male patients had severe deficiency of Vitamin D3. However, there was no significant difference between the baseline Vitamin D3 levels of either gender. The mean + SD 25-hydroxycholecalciferol levels at baseline, 4 weeks, and 12 weeks after completion of treatment were 14.4+6.69 ng/dl, 62.04+21.88 ng/dl, and 27.24+7.84 ng/dl respectively. At 4 weeks after completion of treatment,127 patients had recovered from Vitamin D3 deficiency of which102 (90.3%) were female and 25 (92.6%) were male patients while, at 12 weeks 43 patients maintained normal levels of the vitamin D of which 34 (30.1%) were female and only 9 (33.3%) were male patients (Table 1).

Table 1: Distribution of Vitamin D3 deficiency according to Gender at Baseline, 4th, and 12th week of treatment.

Gender	Mild Deficiency (21-30 ng/dl)	Moderate Deficiency (10-20 ng/dl)	Severe Deficiency (<10 ng/dl)
At Baseline			
Male	4 (14.8%)	14 (51.9%)	9 (33.3%)
Female	26 (23.0%)	47 (41.6%)	40 (35.4%)
p = 0.539			
At 4 weeks			
	Normal (>30 ng/dl)	**Mild Deficiency (21-30 ng/dl)**	**Moderate Deficiency (10-20 ng/dl)**
Male Female	25 (92.6%) 102 (90.3%)	2 (7.4%) 9 (8.0%)	0 (0.0%) 2 (1.8%)
p = 0.779			
At 12 weeks			
	Normal (>30 ng/dl)	**Mild Deficiency (21-30 ng/dl)**	**Moderate Deficiency (10-20 ng/dl)**
Male Female	9 (33.3%) 34 (30.1%)	14 (51.9%) 63 (55.8%)	4 (14.8%) 15 (13.3%)
p = 0.938			

One-month post-treatment levels of 25-hydroxycholecalciferol were measured. It was found that, 45 (94%) patients in oral group, 38 (83%) patients in Injection formulation given orally group and 44

 doi.org/10.36283/PJMD9-1/005

(96%) patients in Intramuscular injection group had attained normal vitamin D levels one-monthafter treatment. Upon comparison, all three routes of administration of Vitamin D were equally efficient with no significant difference between the routes.- Three months post-treatment of 127 patients who had achieved the vitamin D levels >30ng/dl their laboratory tests were repeated. It was found that only 15 (33%) patients in oral group, 11 (29%) patients in Injection formulation given orally group and 17 (39%) patients in Intramuscular injection group had maintained their vitamin D levels within the accepted normal range of >30 ng/dl. There was no significant difference between the three routes (Table 2).

Table 2: Patients with Normal Level of Vitamin D Intensity after 4 weeks and 12 weeks.

Vitamin D levels	Oral Group (n=48)	Injection Formulation Given Oral Group (n=46)	Intramuscular Injection Group (n=46)	Total (n=140)
>30 ng/dl	45 (94%)	38 (83%)	44 (96%)	127 (91%)
<30 ng/dl	3 (6%)	8 (17%)	2 (4%)	13 (9%)
p-value = 0.06				
Vitamin D levels	**Oral Group (n=45)**	**Injection Formulation Given Oral Group (n=38)**	**Intramuscular Injection Group (n=44)**	**Total (n=127)**
>30 ng/dl	15 (33%)	11(29%)	17 (39%)	43 (34%)
<30 ng/dl	30 (67%)	27 (71%)	27 (61%)	84 (66%)
p-value = 0.64				

DISCUSSION

The current study evaluated the efficiency of three different routes and found that all routes of administration was equally effective (whether it is oral formulation, Injection formulation given orally, or intramuscular injection regimens) in treating vitamin D deficiency. It also showed that the selected protocol for replacement was adequate in correcting vitamin D deficiency. At one month after completion of the treatment, the majority of the patients had attained normal Vitamin D levels. However, three-month post-treatment results showed significant recurrence of vitamin D deficiency among the patients. Our study showed no significant difference among the three different routes for administration of 25-hydroxycholecalciferol in patients with deficiency.

In a similar study conducted on elderly patients with vitamin D deficiency, the efficacy of oral and intramuscular routes was compared and assessed . It was reported that a single large dose of Vitamin D3 was sufficient to significantly increase vitamin D levels with the majority of the patients reaching adequate levels by the end of the study. It was reported that both routes of administration were equally effective and safe, but Intramuscular injection route was found more effective in maintaining 25-hydroxycholecalciferol levels . In the present study, there was no significant difference between the efficacies of the three different routes of administration. This could be explained by the amount of each dose prescribed and by patient compliance. Another theory to support this observation, proposed by Mawer et al. is that oral dose is associated with lipoproteins, it enters the hepatic circulation to be metabolized by hepatic 25-hydroxylase while remaining product is inactivated[12]. This can explain the greater but more transient serum 25-hydroxycholecalciferol increase after a single oral dose of Vitamin D3.

In another randomized clinical trial, 92 participants with vitamin D deficiency were assigned to receive 300,000 IU of vitamin D3, either orally in six divided doses during 3 months period or as a single Intramuscular injection[13]. Similar to our study, it also concluded that both treatment regimens significantly increased the serum 25-hydroxycholecalciferol level. However, the change in vitamin D levels at month 3 were significantly higher in oral than the Intramuscular injection group (p=0·03). Whereas, in our study the levels reduced significantly by the 12th week on follow-up irrespective of the route of administration. This could be because the study in question, distributed the amount of oral medicine into six equal dosages, which may have taken up more time to metabolize as compared to a single dose of Intramuscular injection.

In the present study, the vitamin D levels were measured at 4 and 12 weeks after completion of the treatment regimes. We report that while all three administrative routes were equally effective none of the routes could maintain the vitamin levels among the patients. It was observed that 12 weeks after complete replacement majority of participant developed Vitamin D deficiency again. The mean vitamin D3 level had fallen from 62.04+21.88 ng/dl at week 4 to 27.24+7.84 ng/dl by week 12 after last dose of vitamin D3. This is in contrast to a study conducted in India in 2017, where a dose of 60,000 IU cholecalciferol (Vitamin D3), given weekly per oral over a period of 5 weeks was compared to a single dose of 300,000 IU given as an Intramuscular injection of Vitamin D3.

It was reported that both oral and Intramuscular injection routes are equally effective for treating the vitamin deficiency, however, a single dose of 300,000 IU given intramuscularly provided a more sustained increase from baseline[14]. This could be because of the deposition of dose at the site of Intramuscular injection which results in a slow but steady response[15]. Similar results were reported in Italy, where researchers evaluated the long-term bioavailability and efficacy of a single high dose of vitamin D3 prescribed either orally or as Intramuscular injection. It was reported that, the oral dose of 600,000 IU of vitamin D was initially more effective in increasing serum 25-hydroxycholecalciferol levels as compared to an equivalent Intramuscular injection dose but was rapidly metabolized and inactivated by the body[16].

A local study of 2015, evaluated the different doses of Vitamin D prescribed to deficient patients with comparison of oral and intramuscular routes of administration. It was revealed that vitamin D deficiency was corrected in more than 70% of participants with a single dose of either 600,000 or 200,000 IU prescribed per oral or as Intramuscular injection[11]. One factor that gives this study superiority over all others is that none of the previous studies has used injection formulation through oral route. To the best of our knowledge, this is the first study that has compared the efficacy of administering Injection formulation given orally in patients with vitamin D3 deficiency.

Few limitations of our study are a shorter follow-up time i.e. 12 weeks and a small sample size. More research and data is needed to draw any evidence-based conclusion regarding the safety, efficacy, and the dose of vitamin D to be prescribed for the treatment of deficiency.

CONCLUSION

In short, all three routes (Oral, Injection formulation given orally and Intramuscular injection) of administration of vitamin D supplement in vitamin deficient patient had the same efficacy with no significant advantage over each other. Further research can shed more light onto this matter.

ACKNOWLEDGEMENTS

We specifically thank General Medical and Orthopedic outpatient clinics of Imam Clinic Hospital, Karachi, Pakistan for allowing and supporting to conduct this research project. We would also like to thank Dr. Saeeda Baig for her immense support and guidance in manuscript writing.

CONFLICT OF INTEREST

There was no conflict of interest among the authors.

ETHICS APPROVAL

The study approval was sort from Imam Clinic Hospital, Ethics Review Committee (Ref. No. 2018/09/001).

PATIENT CONSENT

Verbal and written informed consent was obtained from all patients.

AUTHORS' CONTRIBUTIONS

All the authors contributed to and collaborated in preparing this paper. SAP and NS conceived the idea. SAP, NS and JA collected the data. JA and FA wrote the manuscript. SAP supervised the project and did critical review. JA, FA, AB and AAK collaborated to final write up.

REFERENCES

1. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CMet. al.Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2011;96: 1911–1930.
2. Mahmoud AA, Ali AH.Vitamin D receptor gene polymorphism and 25 hydroxy vitamin D levels in Egyptian patients with pulmonary tuberculosis. Egypt J Chest Dis Tuberc. 2014;63: 651–655.
3. Saad K, Abdel-rahman AA, Elserogy YM, Al-Atram AA, Cannell JJ, Bjørklund G, Abdel-Reheim MK, Othman HA, El-Houfey AA, Abd El-Aziz NH, Abd El-Baseer KA. Vitamin D status in autism spectrum disorders and the efficacy of vitamin D supplementation in autistic children. Nutri Neurosci. 2016;19(8):346-51.
4. Kočovská E, Fernell E, Billstedt E, Minnis H, Gillberg C. Vitamin D and autism. Clinical review. Res Dev Disabil. 2012;33: 1541-1550
5. Anjum I, Jaffery SS, Fayyaz M, Samoo Z, Anjum S. The role of vitamin D in brain health: a mini literature review. Cureus. 2018;10(7).

6. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014;144 (Pt A):138–145.
7. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA, El-Hajj Fuleihan G, Josse RG, Lips P, Morales-Torres J. IOF Committee of Scientific Advisors (CSA) Nutrition Working Group, Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int. 2009;20(11):1807–1820.
8. Natasja M, Lips P. Worldwide vitamin D status. Best Pract Res Clin Endocrinol Metab. 2011; 25:671-80.
9. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. Am J Clin Nutr. 2008; 87(4):1080S–1086S
10. Zuberi LM, Habib A, Haque N, Jabbar A. Vitamin D deficiency in ambulatory patients. J Pak Med Assoc. 2008; 58:482-4
11. Mansoor S, Habib A, Ghani F, Fatmi Z, Badruddin S et al. Prevalence and significance of vitamin D deficiency and insufficiency among apparently healthy adults. Clin Biochem. 2010; 43:1431-5.
12. Tellioglu A, Basaran S, Guzel R, Seydaoglu G. Efficacy and safety of high dose intramuscular or oral cholecalciferol in vitamin D deficient/insufficient elderly. Maturitas. 2012;72(4):332-8
13. Masood MQ, Khan A, Awan S, Dar F, Naz S, Naureen G, Saghir S, Jabbar A. Comparison of vitamin D replacement strategies with high-dose intramuscular or oral cholecalciferol: a prospective intervention study. Endocr Pract. 2015;21(10): 11 25-33.
14. Mawer EB, Backhouse J, Holman CA, Lumb GA, Stanbury SW. The distribution and storage of Vitamin D and its metabolites in human tissues. Clin Sci.1972;43:413-31.
15. Zabihiyeganeh M, Jahed A, Nojomi M. Treatment of hypovitaminosis D with pharmacologic doses of cholecalciferol, oral vs intramuscular; an open labeled RCT. Clin Endocrinol. 2013;78(2):210-6.
16. Gupta N, Farooqui KJ, Batra CM, Marwaha RK, Mithal A. Effect of oral versus intramuscular Vitamin D replacement in apparently healthy adults with Vitamin D deficiency. Indian J Endocrinol Metab. 2017;21(1):131.
17. Whyte MP, Haddad JG Jr., Walters DD, Stamp TC. Vitamin D bioavailability: Serum 25-hydroxyvitamin D levels in man after oral, subcutaneous, intramuscular, and intravenous Vitamin D administration. J Clin Endocrinol Metab.1979;48:906-11.
18. Cipriani C, Romagnoli E, Pepe J, Russo S, Carlucci L, Piemonte S, Nieddu L, McMahon DJ, Singh R, Minisola S. Long-term bioavailability after a single oral or intramuscular administration of 600,000 IU of ergocalciferol or cholecalciferol: implications for treatment and prophylaxis. J Clin Endocrinol Metab.2013;98(7):2709-15.