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A STUDY TO SHOW THE EFFECT OF VITAMIN D3 ON EFFICACY OF ANTI-TUBERCULAR THERAPY (ATT) / DIRECTLY OBSERVED TREATMENT, SHORT COURSE (DOTS) REGIMEN.

Pharmacology

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ABSTRACT

INTRODUCTION : Pulmonary tuberculosis is one of the largest causes of deaths due to infections worldwide. WHO recognizes India as one of the 22 high-burden countries (HBC's) that account for about 80% of the world's TB cases. The evidence for role of Vitamin D3 on the course of tubercular disease is inconclusive and different studies show both favorable and unfavorable responses. No data is available on dose-dependent effects of vitamin D3 on mycobacterial activity.

MATERIAL AND METHODS: A prospective, randomized, interventional study of 90 days duration was conducted by dividing 60 newly diagnosed sputum positive pulmonary tuberculosis Category I patients of either sex with age ≥16 years in two groups i.e
Group A receiving standard Anti-tubercular therapy in combination with
Vitamin D3 600,000IU intramuscularly on Day 0, 30 and 60 and Group B receiving standard Anti-tubercular therapy (DOTS regime) alone.

RESULTS: Out of 60 subjects enrolled in the present study, 39 (65%) patients were from urban, and 21 (35%) patients were from rural population. All the patients enrolled in the study belonged to Below Poverty Line (BPL) group. In Group A and Group B, there was statistically significant increase in mean difference in body weight at 30, 60 and 90 days from the baseline within the groups. No difference was found in 0 to 90 days among Group A and Group B. There was statistically significant increase in Vitamin D levels in Group A only on 90 days. At 90 days, there was significant difference in Vitamin D levels between Group A and Group B.

KEYWORDS

INTRODUCTION

Pulmonary tuberculosis is a highly communicable infectious, chronic granulomatous disease of lungs caused by Mycobacterium tuberculosis bacilli (Mtb). It is one of the largest causes of deaths due to infections worldwide, and among the oldest diseases known to mankind.

Pulmonary Tuberculosis is associated with high morbidity and mortality. Globally, there were an estimated 9.6 million new TB cases with 1.5 million TB deaths in 2014.1 In India, an incidence of 2.2 million cases, and prevalence of 2.5mn of TB were reported in 2014. Pulmonary bacteriologically confirmed new TB cases notified in 2014 were 754,268 in India1, and 23,864 in Punjab.2

WHO recognizes India as one of the 22 high-burden countries (HBC's) that account for about 80% of the world's TB cases. India alone accounts for the 26% of TB cases globally, and ranks 17th among 22 HBC's in terms of TB incidence rate. Approximately 1.44 million patients are registered for treatment with Revised National Tuberculosis Control Programme (RNTCP) in 2014.3

In 1993, WHO declared tuberculosis as a global emergency. RNTCP took its route in India in 1993. The main aim of RNTCP using DOTS strategy is to cure at least 85% new sputum smear positive patients and to detect 70% of these new cases in community.4

In India, majority of the population have been found to have vitamin D_3 deficiency.[5] A series of studies from different parts of India have correlated this deficiency with an increased incidence of severity of TB and MDR-TB.[6] Vitamin D_3 has been found to have an immunomodulatory role, and it enhances the formation of autophagosome, helping host cells in killing Mtb.[7]

The evidence for role of Vitamin D_3 on the course of tubercular disease is inconclusive and different studies show both favorable and unfavorable responses. No data is available on dose-dependent effects of vitamin D_3 on mycobacterial activity.[8] The effect of vitamin D_3 supplementation on early sputum conversion to reduce the spread of TB needs to be evaluated.

MATERIAL AND METHODS

A prospective, randomized, interventional study of 90 days duration was conducted in the Department of Pharmacology in collaboration with Department of Tuberculosis and Respiratory Diseases, Government Medical College, Amritsar. 60 newly diagnosed sputum positive pulmonary tuberculosis Category I patients of either sex with age ≥16 years were enrolled from the out-patient department. They were divided randomly in two groups A and B, comprising of 30 patients each.

Group A: In this group, the patients received standard Anti-tubercular therapy (Directly Observed Therapy, Short-course regimen DOTS) in combination with Vitamin D_3 600,000IU intramuscularly on Day 0, 30 and 60.

\Group B: In this group, the patients received standard Anti-tubercular therapy (DOTS regime) alone.

The approval of ethics committee was taken before the start of study. Written informed consent was taken from patients. Patients were advised to report any adverse effect with drug treatment, which were managed accordingly. If modification of DOTS therapy was required, the patient was excluded from the study.

INCLUSION CRITERIA

Newly diagnosed sputum positive pulmonary TB patients of either sex ≥16 years of age

EXCLUSION CRITERIA

Based upon clinical history, the patients with the following conditions were excluded:

a) Extra-pulmonary TB
b) Human Immunodeficiency Virus (HIV) infection.
c) Pregnant and lactating females
d) Hepatic and renal diseases
e) Cardiac disorders
f) Concomitant Diabetes Mellitus (DM)
g) Over weight
h) Gout
i) Current consumption of vitamin D (within two months)
j) Patients on drugs interacting with metabolism of Vitamin D_3, immunosuppressives
k) Recent trauma or surgery
l) Hyperthyroidism
m) Malignancy
n) Sarcoidosis
o) All the included patients completed the study and were statistically analyzed. The observations were tabulated in the form of mean ± standard deviation (SD) and analyzed using 't' test; paired `t`-test for intra-group comparison and unpaired `t` test for inter-group comparison and level of significance was determined as its 'p' value with
p) p>0.05 -- insignificant

q) p<0.05 -- significant

OBSERVATIONS:

Out of 60 subjects enrolled in the present study, 39 (65%) patients were from urban, and 21 (35%) patients were from rural population. All the patients enrolled in the study belonged to Below Poverty Line (BPL) group (Table I). Table II shows In Group A and Group B, there was statistically significant increase in mean difference in body weight at 30, 60 and 90 days from the baseline within the groups. No difference was found in 0 to 90 days among Group A and Group B. There was statistically significant increase in Vitamin D levels in Group A only on 90 days. At 90 days, there was significant difference in Vitamin D levels between Group A and Group B (Table III).

Table I: Urban/rural Distribution Of Subjects

GROUP	URBAN	RURAL
A	20	10
B	19	11

Table Ii: Mean Change In Body Weight At 0, 30, 60 And 90 Days

Body Weight (Kg)				
	Group A		Group B	
	Mean	SD	Mean	SD
Day 0	50.7	10.87	47.93	11.15
Day 30	51.66	10.58	48.56	11.14
Day 60	52.21	10.48	49.25	11.22
Day 90	52.93	10.45	49.91	11.30
p-value				
	Group A	Group B		
0-30 days	<0.05	<0.05		
0-60 days	<0.05	<0.05		
0-90 days	<0.05	<0.05		

TABLE III: MEAN CHANGE IN VITAMIN D AT 0, 30, 60 AND 90 DAYS

Vitamin D levels (nM)				
	Group A		Group B	
	Mean	SD	Mean	SD
Day 0	29.93833	10.36	26.52373	13.89
Day 90	49.76901	8.448995	28.08	12.71
p-value				
	Group A	Group B		
0-90 days	<0.05	0.1290		

DISCUSSION :

The effect of vitamin D_3 supplementation have been studied as an adjuvant on safety and efficacy of anti-tubercular therapy (ATT) / Directly Observed Treatment Short Course (DOTS) regimen given as per RNTCP guidelines.

BODY WEIGHT

In the present study, a statistically significant increase in body weight was observed at 30, 60 and 90 days from baseline in both Groups A and B (*p-value* < 0.05Table II). But there was no statistically significant mean difference (3.01 Kg) in body weight among Group A and B (*p-value* 0.287 Table II).

A double-blind, randomized, placebo controlled trial conducted by Wejse *et al.* (2009) which recruited 365 patients, and 100,000IU cholecalciferol vs placebo were given in addition to ATT; also reported similar observations with significant increase in body weight within the groups, but statistically non-significant mean difference in body weight among the two groups.[8] Hence, Vitamin D_3 supplementation did not increase the weight gain of patients.

Contrary to this, in a randomized placebo-controlled study conducted by Salahuddin *et al.* (2013) in Pakistan reported statistically significant increase in body weight i.e. + 3.75 (95% CI 3.16 – 4.34) in vitamin D_3 supplemented group v/s + 2.61 (95% CI 1.99 – 3.23) in the placebo group (*p-value* 0.009). Vitamin D_3 was used in the dose of 600,000 IU for 2 doses one month apart.[9]

VITAMIN D_3 LEVELS

There was statistically significant increase in Vitamin D levels in Group A over 90 days duration respectively with *p-value*<0.05. At 90 days, there was significant difference in Vitamin D levels between Group A and B with *p-value*<0.05 (Table III).

The above observations are similar with a study conducted by Daley *et al.* (2015) where 100,000 IU of Vitamin D_3 (2·5 mg dose of vitamin D_3 orally) was given to test group. The concentration in the vitamin D group increased significantly by 14.2 nmol/L (*p-value* 0·001) from baseline vs 6·66 nmol/L in the placebo group (*p-value* 0·15), though, even the patients who received vitamin D were unable to achieve sufficiency.10 Another double-blind randomized study conducted by Martineau *et al.* (2011) where same dose was used as by Daley *et al.* (2015), but was given at 0, 2, 4 and 6 weeks along with ATT in test group *vs* placebo in control group; reported mean serum Vitamin D at 8 weeks to be 101.4 nmol/L vs. 22.8 nmol/L in intervention vs. placebo arms respectively (95% CI for difference 68.6 - 88.2 nmol/L, *p-value*<0.001).[11]

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