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A RANDOMIZED CONTROL TRIAL TO ASSESS VITAMIN "D" SUPPLEMENTATION EFFICACY ON SMEAR POSITIVE PULMONARY TUBERCULOSIS (PTB) PATIENTS

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Abstract:
Objective: *We aimed to determine Vitamin "D" supplementation efficacy in order to achieve earlier conversion of sputum in a deficiency of Vitamin "D" smear-positive patients diagnosed with pulmonary tuberculosis (TB).*
Methods: *Our randomized clinical trial (RCT) was carried out on 120 sputum smear-positive pulmonary tuberculosis patients at Allied Hospital, Faisalabad (August 2016 to July 2017). Two groups were made out of random sampling technique as Group A and B. Group "A" was managed with ATT (Anti-Tuberculous Therapy); whereas, Group "B" was managed with Vit "D" Supplementation along with ATT. In the intensive phase after every fourteen days patients were managed with (100,000 IU Vit "D") through intramuscular injection. After every second, fourth, eighth, tenth and twelfth week we repeated sputum assessment. Chi-Square test was applied for the assessment of treatment efficacy in the earlier conversion of sputum between Group A and B for the comparison of Vit "D" mean values pre and post-treatment ($p \leq 0.05$).*
Results: *Group A and B had a respective mean age of (37.18 ± 6.81) and (39.02 ± 7.56) years. We included 63 males (52.50%) and 57 females (47.50%). Group A and B had a mean value of serum Vit "D" as (17.07 ± 1.44) and (17.23 ± 2.37) as baseline values. After 12 weeks these values were (21.77 ± 2.23) and (29.24 ± 0.72) for Group A and B respectively. Positive sputum assessment was observed as 7 cases (11.7%) in A group and 1 case (1.7%) in the B group with a significant P-value of (0.028).*
Conclusion: *In the intensive phase after every fourteen days patients were managed with (100,000 IU Vit "D") through intramuscular injection. With the intervention of four doses, Vit "D" efficiency was improved and the conversion of sputum smear was also improved in pulmonary tuberculosis (PTB) patients.*
Keywords: *Sputum Conversion, Pulmonary Tuberculosis (PTB), Vitamin D (Vit "D") and Anti-Tuberculous Therapy (ATT).*

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INTRODUCTION:

Tuberculosis (TB) 9th major death cause worldwide which is also above AIDS / HIV [1]. The death count is increasing day by day as it was reported as 1.3 million deaths back in 2016. TB was reported in adults (90%) with females as (35%) and males (65%) back in 2016. HIV cases are reported as 56% in Pakistan, Indonesia, India, Philippines and China [1, 2]. Numerous factors such as HIV, AIDS, overcrowd, socioeconomic status and malnutrition are contributing to the incidence of TB in underdeveloped countries like Pakistan [2, 3].

Vit "D" is responsible to maintain macrophages and monocytes function that is associated with the human immune system and it is important for the pathogenesis. Vit "D" works on affected cells in combination with nuclei receptor; so, functional abnormality and low level of Vit "D" adds in the alteration of the immune system against tubercle bacillus [4]. Vit "D" deficiency is reported in every second person all over the world (50%) [5]. This deficiency is actually reduced ultraviolet exposure which poses higher risks of active TB [4, 6]. PTB patients face 87% Vit "D" deficiency [5]. Mycobacterium tuberculosis (MTB) eradication is the objective of treatment, which can be achieved through Vit "D" level maintenance [6]. Recently a research has managed PTB with (100,000 IU Vit "D") through intramuscular injection of four doses to improve the efficacy of Vit "D" and the conversion of sputum smear in a minimum of seven days [7].

TB in Pakistan is very much resistant against ATT drugs. Hence, it is necessary to find out effective Vit "D" supplementation to achieve conversion of early sputum in smear-positive PTB cases. It will help in the future treatment of PTB cases and in the establishment of Vit "D" supplementation efficacy to manage PTB and achieve sputum conversion.

We aimed to determine Vitamin "D" supplementation efficacy in order to achieve earlier conversion of sputum in a deficiency of Vitamin "D" smear-positive patients diagnosed with pulmonary tuberculosis (TB).

METHODS:

Our randomized clinical trial (RCT) was carried out on 120 sputum smear-positive pulmonary tuberculosis patients at Allied Hospital, Faisalabad (August 2016 to July 2017). Two groups were made out of random sampling technique as Group A and B. Group "A" was managed with ATT (Anti-Tuberculous Therapy); whereas, Group "B" was managed with Vit "D" Supplementation along with ATT. In the intensive phase after every fourteen days patients were managed with (100,000 IU Vit "D") through intramuscular injection. After every second, fourth, eighth, tenth and twelfth week we repeated sputum assessment. Chi-Square test was applied for the assessment of treatment efficacy in the earlier conversion of sputum between Group A and B for the comparison of Vit "D" mean values pre and post-treatment ($p \leq 0.05$). The sample was selected with purposive non-probable technique having confidence as (90%), absolute precision as (9%), expected Vit "D" percentage as (100%) and in 76.7% in Placebo group.

We included all the above eighteen years patients who were recently diagnosed with PTB through a positive AFB (Acid-Fast Bacilli), Chest X-Ray and sputum smear. All extrapulmonary TB or MDR-TB (Multidrug-Resistant Tuberculosis), lactating or pregnant females, serum calcium (> 10.5) mg/dL, renal stones history, renal or liver disorder, previously ATT patients, steroids, cytotoxic, antiepileptics or immunosuppressive drug intake cases were not included in the research.

Ethical approval, informed consent and demographic information were also obtained. Baseline characteristics of Blood CP, blood sugar fasting, serum creatinine, LFT, serum Vit "D" and calcium levels were documented. Patients of A group were treated with rifampicin, weight-based anti-TB (INH 300 mg), ethambutol and pyrazinamide, for three months before breakfast on daily basis in the intensive phase and in continuation phase daily 600 mg rifampicin for six months. Patients of A group were treated with rifampicin, weight-based anti-TB (INH 300 mg), ethambutol and pyrazinamide, for three months before breakfast on daily basis in the intensive phase and in continuation phase daily four doses of intramuscular Vit "D" injection (100,000 IU) fortnightly with 300 mg (INH) and 600 mg (rifampicin) for a period of six months. We dropped all the patients with increased levels of serum creatinine and transaminitis. Levels of serum Vit "D" and serum calcium were also done at the third month. Every information was documented on a Performa. Data analysis was carried out in SPSS software ($P \leq 0.05$).

RESULTS:

We included all the above eighteen years patients who were recently diagnosed with PTB through a positive AFB (Acid-Fast Bacilli), Chest X-Ray and sputum smear. All extrapulmonary TB or MDR-TB

(Multidrug-Resistant Tuberculosis), lactating or pregnant females, serum calcium (> 10.5) mg/dL, renal stones history, renal or liver disorder, previously ATT patients, steroids, cytotoxic, antiepileptics or immunosuppressive drug intake cases were not included in the research. Group A and B had a respective mean age of (37.18 ± 6.81) and (39.02 ± 7.56) years. We included 63 males (52.50%) and 57 females (47.50%). Group A and B had a mean value of serum Vit "D" as (17.07 ± 1.44) and (17.23 ± 2.37) as baseline values. After 12 weeks these values were (21.77 ± 2.23) and (29.24 ± 0.72) for Group A and B respectively. Positive sputum assessment was observed as 7 cases (11.7%) in A group and 1 case (1.7%) in the B group with a significant P-value of (0.028). Every patient completed his treatment. Detailed outcomes analysis can be viewed in the tabular data.

Table – I: Comparison of laboratory Investigations in both groups at different visits

Laboratory Investigations		Study groups	Mean	SD	p-value
Hemoglobin (gm/dl)	At 1st visit (Baseline)	A	12.92	1.04	< 0.001
		B	11.69	1.35	
	At 12th week	A	14.26	0.75	0.154
		B	14.08	0.63	
White Blood Cells (cells/mm3)	At 1st visit (Baseline)	A	9.5983	1.93509	< 0.001
		B	7.4283	2.56434	
	At 12th week	A	5.6267	0.36354	0.683
		B	5.6	0.34933	
Serum calcium (mg/dl)	At 1st visit (Baseline)	A	9.01	0.39	< 0.001
		B	8.8	0.22	
	At 12th week	A	9.43	0.11	0.182
		B	9.4	0.14	

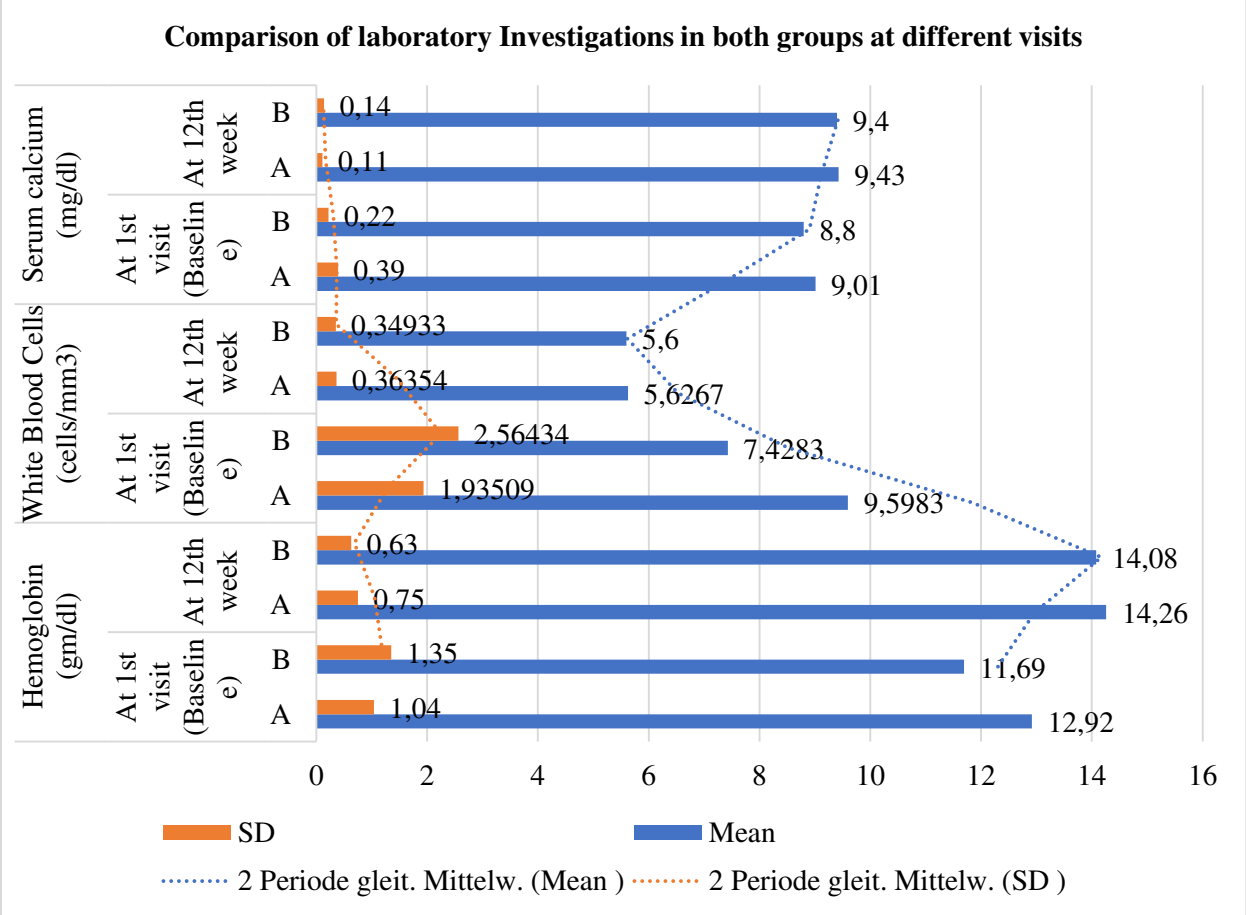


Table – II: Comparison of mean Vitamin D levels in both groups

Vitamin D Study levels (ng/ml)	Study Group	Mean	±S.D	P-value
First visit (Baseline)	A	17.07	1.44	0.056
	B	17.23	2.37	
Second Visit (12th week)	A	21.77	2.23	< 0.001
	B	29.24	0.72	

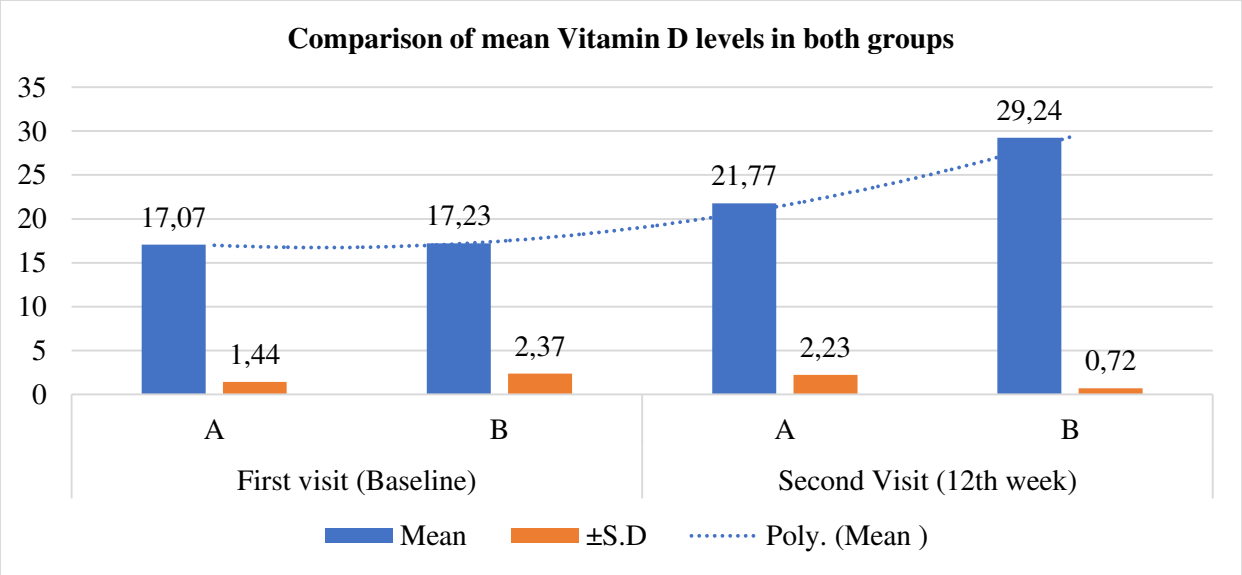
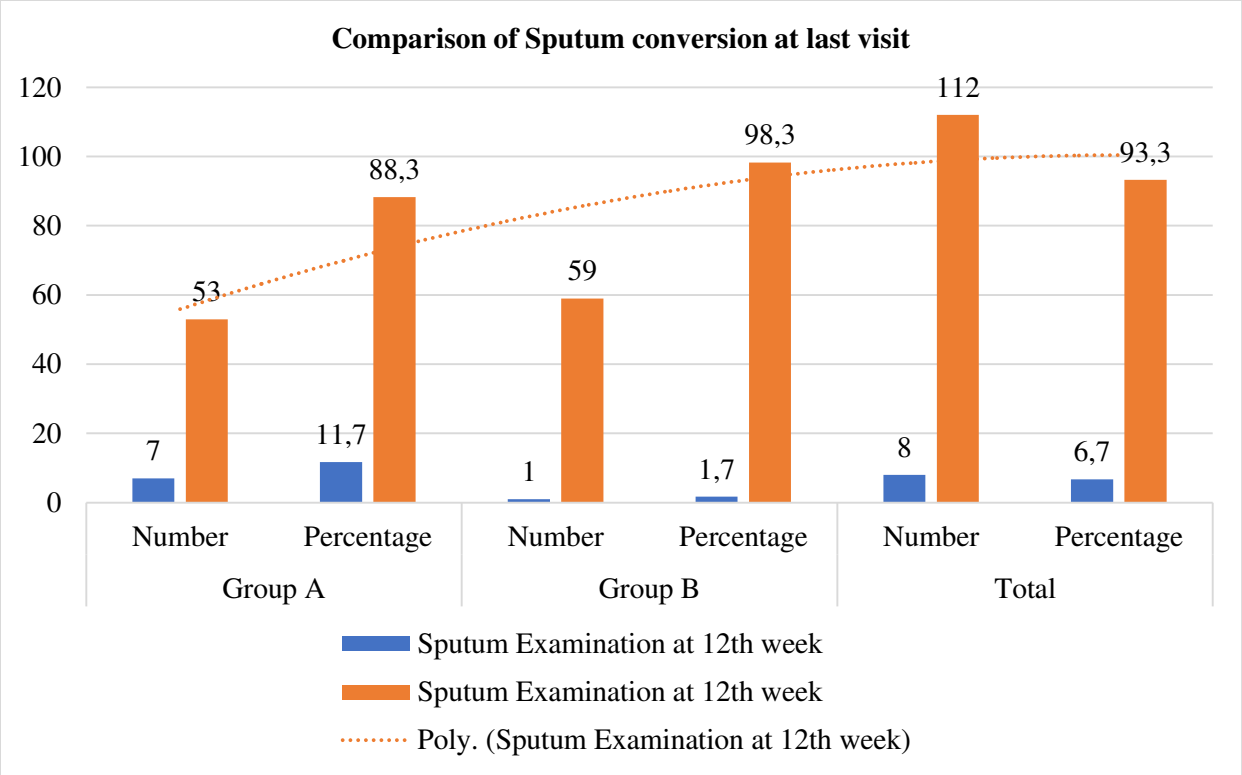


Table – III: Comparison of Sputum conversion at last visit

Comparison		Group A		Group B		Total		P-Value
		No	%	No	%	No	%	
Sputum Examination at 12th week	Positive	7	11.7	1	1.7	8	6.7	0.028
	Negative	53	88.3	59	98.3	112	93.3	
Total		60	100	60	100	120	100	



DISCUSSION:

Poor nutrition, low socioeconomic status, inadequate sunlight in the houses, worse sanitation, illiteracy, malnutrition and low BMI were considered as risk factors for PTB [8 – 10]. These factors may induce PTB and other associated diseases as the level of haemoglobin is reduced [11, 12]. PTB and Vit "D" deficiency have a momentous association as reported by various studies [13 – 15]. Group A and B had respective mean Vit "D" value as (17.07) and (17.23) ng/ml as reported in our research which clearly depicts Vit "D" deficiency. Various other studies also report the same with ATT, especially with an influence of rifampicin and isoniazid on the metabolism of Vit "D" which is a cause of low levels of Vit "D" during treatment [5, 16]. Decreased Vit "D" levels may cause a slight increase in calcium level [17, 18]. Nursyam reported microscopic AFB improvement in conversion of sputum with Vit "D" supplementation (0.25 mg) daily in the treatment (intensive phase) [11].

Kota treated PTB with calcium and Vit "D" (60,000 IU / week) to decrease sputum conversion [19]. Salahuddin also assessed the Vit "D" supplementation effect on 259 patients [20]. Outcomes revealed weight gain by Vit "D" supplementation and decreased disease incidence as observed through Chest (X-ray). Sputum clearance was also observed in our research outcomes at the twelfth week in A group without Vit "D" intake. No proven role has been established by various other authors about PTB treatment by Vit "D" supplementation [18, 21 – 23].

Outcomes established through microscopic evaluation showed significant variations in mean days count mandatory for microscopic AFB sputum conversion with Vit "D" and placebo respectively 49 and 61 days (P-value = 0.032). Vit "D" group was managed well for PTB than placebo after the 12th day of treatment. We focused patients than day count to verify sputum conversion. Positive sputum assessment was observed as 7 cases (11.7%) in A group and 1 case (1.7%) in B group with a significant P-value of (0.028) (p = 0.028).

There is an important preventive role of Vit "D" supplementation to treat PTB. Coussens AK also performed a clinical trial research in order to validate immunomodulatory effects on PTB patients with the administration of Vit "D" [24]. Outcomes reflected the improvement in treatment induced lymphopenia resolution, hyper-cytokinaemia, mono-cytosis and hyper-chemokinaemia. All the above-stated outcomes validate the implementation of Vit "D" as a treatment for PTB patients as it has a positive healing role.

CONCLUSION:

Vit "D" supplementing is recommended by researchers for the smear-positive PTB patients with deficiency of Vit "D". In the intensive phase after every fourteen days patients were managed with (100,000 IU Vit "D") through intramuscular injection. With the intervention of four doses, Vit "D" efficiency was improved and the conversion of sputum smear was also improved in pulmonary tuberculosis (PTB) patients.

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