Section A-Research paper

Arginine rich food supplementation and its clinical effect on C Reactive Protein, ESR and Smear Conversion Rate of Pulmonary Tuberculosis patients.

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ABSTRACT

Overcrowding and poverty are contributing factors for impaired immunity in tuberculosis, studies suggest that malnutrition is triggering factor. A controlled clinical trial was conducted to investigate whether an arginine adjuvant therapy with *Arachis hypogea* (peanuts) could lead to a clinical improvement in smear positive TB patients comparing the outcome on smear conversion, C Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR). Smear positive and symptoms suggestive of active pulmonary tuberculosis (n=196) consisting of 98 patients with peanut administration and Directly observed Therapy short course (DOTs) therapy in study group and the other 98 as controls without peanut administration and on only DOTs therapy were chosen as control for present study. ESR, CRP and Acid fast bacilli (AFB) grading by microscopy were recorded at baseline, two weeks and one month after initiating the treatment regimen in both study and controls. Data was analyzed in SPSS V25. Smear conversion rate was markedly high, ESR and CRP levels noted were specific for each individual that had clinical improvement but did not show any statistical significance. Further studies can be conducted to evaluate the complete role of arginine food supplementation in early recovery of tuberculosis so that in under developed and developing countries like India, the nutritional supplement in the form of peanuts will be a boon.

KEY WORDS:

Arachis hypogea, C Reactive Protein (CRP), DOTs therapy, Erythrocyte Sedimentation rate (ESR), *Mycobaterium tuberculosis*, Smear Conversion.

INTRODUCTION:

The nation with poverty, overcrowding and malnutrition has always shown a prevalence of pulmonary disease called tuberculosis caused by *Mycobaterium tuberculosis*. Still the research is

under process to know the contribution of malnutrition and its influence on tuberculosis (TB). [1] In the recent years, HIV has been proved as an additional predisposing factor for the onset of active TB that had a noticeable effect on cell mediated immune response against the disease. Another research perspective reveals that malnutrition has been a trigger to an impaired immune response against *Mycobacterium tuberculosis*. In ancient days when chemical therapeutic agents were not available, therapy with nutritional intervention was the most harmless, reliable regimen, but the marked contribution of the food supplementation alone to cure TB in this period was always a controversy.[1-4] The amino acid arginine in T-helper lymphocytes type 1 (Th1) - activated macrophages through the high output enzyme inducible nitric oxide (NO) synthase produces high levels of NO that can be measured directly in the exhaled air as well as by the stable urinary metabolites, nitrite and nitrate.[5-7] The production of NO in human infection of tuberculosis is proven but its role in host defense is still a research under debate. [7-9] There are some recent interventional results that favor the disease outcome was followed by micronutrient supplementation and few studies report that there was weight gain but no effect on clinical outcome from nutritional supplementation during treatment against TB, research in this field is still a lacunae by performing controlled clinical studies on macronutrients.[10,11] The present study was conducted as a controlled clinical trial to investigate whether the adjuvant therapy with arginine rich food administration as supplement in the form of peanuts could result in the clinical improvement in pulmonary tuberculosis by analysing the smear conversion rate, erythrocyte sedimentation rate and CRP.

AIM: To study the effect of *Arachis hypogea* (Peanut) administration as adjuvant supplementation along with DOTS therapy in smear positive pulmonary tuberculosis patients and to observe the clinical outcome.

MATERIALS AND METHODS:

This comparative study was performed in smear positive TB with clinical symptoms suggestive of active pulmonary tuberculosis (n=196) consisting of 98 patients with peanut administration and Directly observed Therapy s (DOTs) therapy in study group and the other 98 as controls without peanut administration and on only DOTs therapy were chosen for the present study.

Inclusion criteria:

The patients aged older than 18 years and smear positive by microscopy as per the guidelines of World Health Organization and Ministry of Health and family welfare, Government of India, for the treatment were included in the study.

Exclusion criteria:

The patients aged above 60 years, with peanut allergy, those in need of hospitalization, pregnancy, HIV, previous treatment for tuberculosis, patients under medical treatment for other causes and drop outs were excluded from the study.

A complete and clear instruction with the purpose of this study was well informed to all the patients chosen for the study in the local language. The oral and written consents were taken

from the pulmonary tuberculosis smear positive patients before including them. This study has approval from the Institutional Ethics Committee.

Newly diagnosed smear positive tuberculosis patients attending the outpatient departments from October 2018 to June 2022 with a final follow up until August 2022 at the designated microscopy centre earlier called Revised National Tuberculosis Control Program (RNTCP) and later renamed as National Tuberculosis Eradication Program (NTEP) at the centre where the research was carried out in a tertiary care hospital. The sputum and blood samples were collected along with a standard laboratory requisition form drafted with initial signs and clinical symptoms like cough, fever, haemoptysis, appetite and weight loss. ESR, CRP and Acid fast bacilli (AFB) grading by microscopy were recorded at baseline, two weeks and one month after initiating the treatment regimen. AFB staining and evaluation was done according to national guidelines. Semi quantitative estimation of CRP was done by latex agglutination test (Beacon diagnostics private limited, Gujarat, India) and ESR was measured be Westegren's method at same intervals of baseline, after two weeks and one month.

After confirmation of sputum smear positivity and prior to the starting of DOTS therapy as per the WHO guidelines, the baseline readings of CRP and ESR were recorded. The treatment protocol was thoroughly explained that contained isoniazid, pyrazinamide, rifampicin and ethambutol during the intensive phase of 2 months followed by isoniazid, rifampicin and ethambutol for an additional 4 months as continuation phase. At the time of initiation of the drug in intensive phase the study group patients (n=98) were supplemented with unpeeled peanuts in soaked and boiled form that contained the highest amount of arginine that equals 1438µg/g. Approximately 30 grams of peanuts were administered as an adjuvant therapy along with DOTS. The control group (n=98) were only on DOTs therapy without nutritional supplement with peanuts. The drug supplementation and peanut administration was supervised daily.

The patients were called for follow up after two weeks and one month of administration of drugs and nutritional supplements. During the follow up visit the sputum smear examination was done using the AFB Staining as per NTEP guidelines, CRP was tested by semi quantitative estimation by latex agglutination test and ESR was done. The initial outcomewas recorded after two weeks, completion of one month are the results were tabulated.

STATISTICALANALYSIS: Data were entered in MS-Excel and analyzed in SPSS V25. Descriptive statistics were represented with percentages for qualitative data, Mean with SD and Median with IQR for quantitative data. Shapiro wilk test was applied to find normality. Friedman test was applied to find the significance from baseline to one month. $P<0.05$ was considered as statistically significant.

RESULTS:

Of the 300 cases of tuberculosis our hospital obtained, 215 individuals tested positive for the disease; of these, 11 had mild, 23 had moderate, and 21 had severe lung disease. 29 cases of pleural effusion, 11 cases of disseminated TB, 3 cases of abdominal TB, and 2 cases of TB lymphopadenopathy were identified among the 45 patients of EPTB. The 29 effusion incidents

included nine additional instances of lung parenchyma involvement. TB meningitis symptoms were seen in four cases of disseminated TB. Men made up 40 of the 55 patients with pulmonary TB cases. The course of lung involvement was identical whether it was mild, moderate, or severe. 15 male and 14 female individuals had pleural effusions.Out of 210 sputum AFB smear positive samples, Peanut administration was initiated in 105 patients and only 98 patients took the complete drug and nutritional (peanuts) dose as advised and hence the drop out patient number was low (6.6%) and the other 105 patients were taken as control group who took only DOTS therapy but only 98 results were taken into consideration to equalize the number with the test group on peanut supplementation. No side effects or adverse reactions were reported during food supplementation.

All the results were summarized and tabulated. Table 1 shows the results of Smear positivity of patients with and without Peanut supplementation. In this the smear conversion rate in the patients that was at the baseline, after two weeks and after one month were recorded. The percentage of 62.9 cases with peanut administration and about 59.8% of controls who were on only dot therapy had smear conversion to negative after one month follow up. No cases were Grade 3 positive with peanut administration after one month but 7.2% of cases remained Grade 3 without peanut administration that had a statistical significance of p value 0.001.

The ESR values in Table 2 where the minimum sedimentation rate at baseline was 22mm per hour and maximum was 66mm per hour. After administration of peanuts in these subjects the minimum value after 2 weeks was 12 and maximum was 52. After one month follow up the minimum value was decreased to min. 10mm per hour and max. was 46 mm per hour. The results were same in both control and test groups. The mean ESR level decreases from 40.77 ± 9.43 to 20.74 ± 7.4 after one month treatment. The clinical improvement and the decrease in ESR was almost similar.

Table 3 shows the effect of peanut adjuvant therapy on CRP levels.At the time of diagnosis, the median and mean CRP values in TB patients were 48 mg/L (IQR: 48) (95% CI: [83.8-130.9]), in both treatment and control group respectively. With the start of treatment, the median and mean CRP concentrations decreased to 24 mg/L (IQR: 24) in treatment group while remain constant in control group (48mg/L) ((95% CI: [14.1-26.4]), respectively. The difference in circulating CRP concentrations between diagnosis and 4 weeks after anti-TB medication was not observed in both non-parametric and parametric comparisons.

There was a noted clinical improvement individually who were administered peanuts and those who were not administered. These values had no statistical significance.Peanut supplemented TB patients showed a considerably higher cure rate in the subgroup analysis (62.8% (61/37) vs. 59.8% (17/32), p = 0.01). These outcomes were validated by multiple logistic regression analysis with age and sex adjustments (Table 4).

DISCUSSION:

In this comparative study, we investigated whether arginine-rich food supplementation with peanuts may reduce the clinical symptoms of smear-positive tuberculosis by increasing nitric

oxide production.s also linked to increased catabolism and decreased food intake. 1 Prior to getting TB, patients in countries with a high population often have low nutritional status. Participants in this study who were diagnosed with smear-positive tuberculosis had BMIs of 16–17 kg/m2, which is clearly below the malnutrition cut off point of 18.5 kg/m2. Due to the nature of the TB illness, food consumption is severely restricted during the first few weeks of treatment, so it is unlikely that this would affect the results of our study. One gram of arginine is administered daily, or one-fifth of the average daily intake in industrialised nations. We chose to follow the same daily dosing regimen for arginine provided as a dietary supplement, equivalent to 1 g of arginine for four weeks, as in Schon et al's study [12]. The four-week treatment term was selected since most patients will have responded to treatment by then and start eating on their own, decreasing the likelihood that a further food supplement will be useful. In the current study, smear positive, CRP levels, and ESR levels were investigated. The people had a greater cure rate due to the high smear conversion. The study's findings were reliable and demonstrated that using peanuts as an adjuvant therapy produced better results. Younger age groups demonstrated the highest benefits and the earliest recovery from the disease. The three variables included in the study varied significantly, and because the smear conversion was substantially high, the individuals had a higher cure rate. The study's findings were reliable and demonstrated that using peanuts as an adjuvant therapy led to improved results. In contrast to a study by Farazi A et al., who claim that there was no substantial smear conversion but a constitutional improvement in symptoms, the current study shows that there was a good smear conversion rate in peanut administered individuals. [13]

The success of tuberculosis treatment has been suggested to be monitored by a number of immune-based biomarkers, such as C-reactive protein (CRP), an acute inflammatory protein and component of the innate immune response [14-19]. Several studies have looked at the usefulness of CRP testing in TB, and they have revealed that TB has a lower median CRP than bacterial pneumonia [20] and that include CRP testing in clinical assessment can assist manage HIV-positive patients in an environment with a high TB incidence rate [21-23]. High baseline CRP levels have also been connected to slow sputum culture conversion [24] and unsuccessful treatment outcomes[25], and it has been discovered that an increase in CRP after 8 weeks of TB treatment is indicative of persistent culture-positive status. In current study, at the time of diagnosis, the median and mean CRP values in TB patients were 48 mg/L (IQR: 48) (95% CI: [83.8-130.9]), in both treatment and control group respectively. With the start of treatment, the median and mean CRP concentrations decreased to 24 mg/L (IQR: 24) in treatment groupwhile remain constant in control group (48mg/L) ((95% CI: [14.1-26.4]), respectively. After one month of treatment, CRP levels remained over the inflammatory threshold even in patients with negative sputum smear results, despite a dramatic drop in those levels.

We found that 87% of people in this study of recently discovered active TB patients had increased ESRs and 26% had normal ones at baseline. Patients with pulmonary TB were reported to have an average ESR of 40.77. In a previous Saudi study, haematological abnormalities were

examined in 50 patients with pulmonary TB and positive sputum smear results [26]. The mean ESR readings were found to be 30.71 and 20.71after two weeks and one month duration respectively, with a range of 12-52 and 10-46 mm/hr. Nevertheless, no information was provided regarding the percentage of patients with ESRs that were normal, above normal, or greater than 100.According to the authors of a study carried out in India [27], a lower ESR value in a TB patient may be associated to HIV infection in a developing country like India, and the higher the ESR value, the lower the risk of a related HIV infection.

In our study there was improvement in ESR and CRP individually showed that there was a good clinical outcome but there was no statistical significance. A study by Gad MZ states that there was an improvement in body mass index, reduced constitutional symptoms and decreased CRP in response with the increased arginine levels, which had ergogenic potential because arginine play a pivotal role in the secretion of endogenous growth hormone and their involvement in the synthesis of creatinine. L-Arginine supplementation affects on CNS function that has increasing effect on nitric oxide and strengthen the immune system. [28] Two separate individual trials that were performed earlier have reported the role of L-arginine in TB, performing the study by testing arginine-rich food (peanuts) supplementation. In the first study, an early sputum smear conversion and recovery from cough were reported in the peanut supplemented group, but this study reported only HIV negative patients. [29] The second study concluded that there was no significant wholesome advantage and reported that better cure rates was observed in HIV positive participants who took the arginine-rich adjuvant therapy. [12] This study results are in concurrence with arandomized clinical trial of TB patients without HIV infection by T Schon et al, supplementation with arginine resulted in higher sputum conversion rates, faster recovery from symptoms and a marked increase in weight. However, this outcome was not seen in patients with Acquired immune deficiency syndrome in the trials that were performed separately. [30] A controversial result was declared by APRalph et al., who have found in their research that the effect of L-arginine along with vitamin D as combined therapy in TB and at the doses that they used in the study,they could not show that these agents alone or in combination were showing significant benefits in TB cure rate. [31] In a research performed by MK Magdy et al., from Cairo, Egypt reported that CRP and ESR showed equal responses in monitoring the therapy and concluded that the smear conversion with first line DOT therapy was about 88% by the end of second month. [32] This study results were almost similar to the present study, but was performed in extra pulmonary cases.

The clinical outcome that happened in TB patients was may be by elevated production of NO which was increased due to arginine consumption in the form of peanuts. The results obtained support a role of peanut administration that can aim at enhancing the human anti mycobacterial effect during the treatment of active tuberculosis.In our study no major side effects were reported in the peanut administered groups.

The important limitation in this study related to the lack of evaluation of arginine utilisation and estimated levels of nitric oxide production in the patients administered with peanuts and also its

effect on other inflammatory markers like interleukins. We propose that further studies can be conducted to evaluate the complete role of arginine in early recovery of the disease. Hence in under developed and developing countries like India that the nutritional supplement in the form of peanuts will be a boon.

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LEGENDS:

Table 1: Smear positivity of patients with and without Peanut supplementation

Table 2: ESR levels of patients at baseline, after two weeks and after one month of peanut administration and without peanut supplementation.

Table 3: CRP levels and their variation at various chosen intervals with and without peanut administration.

Table **1:**

SMEAR POSITIVITY	Grading	Test (n=98)		Control (n=98)		P-value
		Count	%	Count	%	
BASELINE	1	21	21.6%	25	25.8%	0.27
	2	19	19.6%	26	26.8%	
	3	57	58.8%	46	47.4%	
TWO WEEKS	0	21	21.6%	10	10.3%	**0.007**
	1	44	45.4%	32	33.0%	
	2	18	18.6%	34	35.1%	
	3	14	14.4%	21	21.6%	
ONE MONTH	0	61	62.9%	58	59.8%	**0.001**
	1	34	35.1%	21	21.6%	
	2	2	2.1%	11	11.3%	
	3	0	0.0%	7	7.2%	

Table 2

ESR		Min. mm/hr	Max. mm/hr	Mean	SD	Median	IQR	P-value
BASELINE	Test	22	66	40.77	9.43	42.00	13	0.22
	Control	22	66	42.47	8.83	42.00	11	
TWO	Test	12	52	30.71	8.41	30.00	12	0.22

WEEKS	Control	12	52	32.35	9.00	32.00	13	
ONE MONTH	Test	10	46	20.74	7.13	20.00	8	0.42
	Control	10	46	21.71	7.73	20.00	9	

Table 3

CRP		Min. µg/dl	Max. µg/dl	Mean	SD	Median	IQR	P-value
BASELINE	Test	12	96	68.16	27.58	48.00	48	0.92
	Control	12	96	68.63	28.32	48.00	48	
TWO WEEKS	Test	6	96	37.18	23.46	24.00	24	0.67
	Control	6	96	38.63	24.12	48.00	24	
ONE MONTH	Test	6	96	19.17	14.89	12.00	12	0.82
	Control	6	96	19.69	16.06	12.00	12	

Table 4: Logistic regression analysis

Parameters	Univariate Analysis	p-value	Multivariate analysis	p-value
TB Culture				
Positive	0.52 (0.46 to 0.58)	<0.001	0.55 (0.47 to 0.64)	<0.001
Negative	Reference			
Age				
<20 years	0.48 (0.37 to 0.62)	<0.001	0.68 (0.46 to 0.99)	0.044
20-35 years	0.94 (0.82 to 1.09)	0.427	0.86 (0.70 to 1.03)	0.104
36-50	1.08 (0.92 to 1.27)	0.351	0.88 (0.72 to 1.08)	0.223
50-60	Reference			
Gender				
Female	Reference			
Male	1.40 (1.24 to 1.58)	<0.0001	1.29 (1.13 to 1.48)	<0.001

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