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Original Research Article

A prospective, open label, randomized study of efficacy of vitamin A as an add on therapy in the clinical outcome of tuberculosis patients

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ABSTRACT

Background: Tuberculosis is the most prevalent infectious disease in the world. India accounts for nearly one fifth of global incidence of tuberculosis. If untreated the disease may be fatal within five years in 50-65 percent of cases. Many decades of research have shown that severe oxidative stress plays a significant role in tuberculosis patients. Moreover, the malnutrition which is commonly present in patient with tuberculosis can add to the impaired anti oxidant capacity. The present study was to investigate the effect of supplementation of vitamin A with standard treatment on the health status of newly diagnosed sputum positive pulmonary tuberculosis patients.
Methods: Phase III, prospective, open, two arm parallel group, outpatient, randomized, active controlled study. Centre of the study was Tuberculosis clinic, Department of Internal medicine, Stanley Medical College Chennai.
Duration of the study was for active drug therapy - 2 months, for follow up period - 4 months and for total period - 6 months.
Results: In our study it was evident that there was a statistically significant improvement in the Karnofsky's score, body mass index, mid upper arm circumference in the in the vitamin A supplementation group when compared to the control group at the end of 2 months and 6 months. And also, a statistically significant decrease in C.R.P. levels and E.S.R levels were also observed.
Conclusions: This study shows that vitamin A as an add on therapy with regular anti-tuberculosis treatment improves the quality of life and decreases the disease activity in pulmonary tuberculosis patients to a greater extent than with routine standard drug therapy alone.

Keywords: Antioxidants, Tuberculosis, Vitamin A

INTRODUCTION

Tuberculosis is the most prevalent infectious disease in the world. It is estimated that about one third of the current global population is infected asymptomatically with tuberculosis; of which 5-10 percent will develop the clinical disease during their life time.[1] Tuberculosis remains a major health problem in India. India accounts for nearly one fifth of global incidence of tuberculosis. Tuberculosis kills more adults in India than any other infectious disease. If untreated the disease may be fatal within five years in 50-65 percent of cases and patients with sputum smear positive pulmonary tuberculosis disease can infect about 10-15 persons in a year.[2] Although anti-mycobacterial treatment meets with a high success rate, resistance towards the first line anti-mycobacterial drugs is increasing. For these reasons, new approaches towards treatment are being looked for.

Many decades of research have shown that severe oxidative stress plays a significant role in tuberculosis patients, indicating a potential role of oxidants in the

pathogenesis of the disease.[3-5] During pulmonary inflammation increased amounts of Reactive Oxygen Species and reactive oxygen intermediates are produced as a consequence of phagocytic respiratory burst. This enhanced Reactive Oxygen Species generation may promote tissue injury and inflammation. This may further contribute to immunosuppression particularly in those with impaired anti-oxidant levels. Moreover, the malnutrition which is commonly present in patient with tuberculosis can add to the impaired anti oxidant capacity.

Study by Karyadi et al, found that zinc and vitamin A deficiency were more prevalent among sputum smear positive tuberculosis patient than in matched healthy controls.[6] Hence the presence of vitamin A deficiency has raised a question whether vitamin A supplementation would give additional benefits for patients with sputum positive pulmonary tuberculosis.

The mechanism of the benefits of vitamin A on the clinical outcome of tuberculosis is yet to be proven. However, it is likely to be related to an influence on the immune system. In experimental and animal models, vitamin A promotes differentiation and cytokine secretion by macrophages and may down regulate the secretion of pro-inflammatory cytokines e.g. TNF-alpha and IL-6. Vitamin A supplementation has been reported to promote lymphogenesis and induce a higher proportion of CD4 naive T-cells.[7]

The present study was to investigate the effect of supplementation of vitamin A with standard treatment on the health status of newly diagnosed sputum positive pulmonary tuberculosis patients.

METHODS

Design of the study was Phase III, prospective, open, two arm parallel group, outpatient, randomized, active controlled study.

Study centre

Tuberculosis clinic, Department of Internal Medicine, Stanley Medical College, Chennai.

Duration of the study was active drug therapy was 2 months, for follow up period was 4 months and for total period was 6 months.

Sample size was 50 patients in each group 100 patients in total.

Inclusion criteria

- Newly diagnosed sputum smear positive pulmonary tuberculosis patients
- Age group 18 - 55 years
- Both sexes

Exclusion criteria

- Extra pulmonary tuberculosis patients
- Sputum smear negative pulmonary tuberculosis patients
- Pregnant and lactating women
- Patients with HIV co- infection
- Patients with chronic medical / surgical illness
- Smokers
- Alcoholics
- Patients with abnormal liver and renal function tests

Strategy

Patients who attended the outpatient department of tuberculosis clinic, Stanley Medical College Hospital were explained in detail about the study procedure, purpose and its benefits. Written informed consent was obtained from the patients willing to participate in the study, in the prescribed format in the regional language prior to the commencement of the study procedure.

Screening and recruitment

Patients who had given written informed consent for participation in the study were screened by medical history, physical examination, anthropometric measurements, Karnofsky score, systemic examination, hematological and biochemical analysis.100 patients who fulfilled the inclusion criteria were recruited for the study.

Randomization

Among the 100 patients, all the odd number patients were given vitamin A in addition to the regular medications [study group] and even number patients were given only the regular medications (control group).

Control group

Isoniazid 600mg + Rifampicin 600mg + Pyrazinamide 2000mg + Ethambutol 1600mg three times a week on alternate days for two months.

Study group

In addition to the above drugs, vitamin A 25000 IU capsule once a week for two months.

Study visits

Patients were assessed periodically for a period of six months by clinical examination, Karnofsky score, Anthropometric measurements- weight, mid upper arm circumference, hematological parameters- haemoglobin, total count, differential count, erythrocyte sedimentation rate and C- reactive protein.

Evaluation

Karnofsky score

Functional capability of the patient was assessed by Karnofsky performance status score.[8]

Table 1: Karnofsky score.

Score	Status
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is needed although death is not imminent
20	Very sick; hospitalization necessary; active supportive treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Nutritional status assessment

Nutritional status was determined based on Anthropometric measurements.

Body weight

Assessed using a weighing scale to the nearest 0.5 kg.

Height

Height was recorded to the nearest 1 cm using stadiometer.

Body mass index

Body mass index was calculated by body weight in kilogram divided by height in m2.

Mid upper arm circumference

Mid upper arm circumference was measured using a flexible measurement tape.

Laboratory investigations

Blood samples were collected between 8.00a.m to 10.00a.m. C-reactive protein was estimated using enzyme-linked immunosorbent assay [ELISA]. Hemoglobin, total count and differential count were analysed using automatic analyzer. Erythrocyte sedimentation rate was assessed using Westergren technique.

Instructions to the patients

The patients were instructed to come weekly to collect the medication. They were advised to take their medicines regularly. The necessity for compliance to the regimen was explained. Any intercurrent minor illness and medication taken for the same was to be reported at the next visit. Any adverse events experienced by the patients were to be reported at the next visit.

Follow up

After two months of active drug therapy, both the control and study groups were followed up for a period of four months.

Data analysis

The data obtained at the end of this study was analysed using SPSS software. Appropriate statistical methods were applied as per requirement. P value ≤ 0.05 was considered significant.

RESULTS

Out of the 126 patients screened, 100 patients who fulfilled the inclusion criteria were recruited for the study. They were randomized into control and study groups. There were 9 drop outs.5 from the control group and 4 from the study group. None of the drop outs were due to adverse effects. 45 patients from the control group and 46 patients from the study group completed the study and were included in the statistical analysis. The majority of patients in the study were in the age group of 20-50 years with high prevalence among males. This was in correlation with the established demographic reports. There was no significant difference in age, sex distribution clinical status and biochemical parameters between the control and the study group.

Table 2: Karnofsky performance score.

	Group				Independent t-test
	Control		Study		
	Mean	SD	Mean	SD	
KPS I	73.33	10.87	71.96	9.80	t=0.63 P=0.52
KPS II	82.22	10.85	86.52	7.66	t=2.18 P=0.03
KPS III	87.11	9.44	95.87	5.80	t=5.34 P=0.001
One way ANOVA F-test	F=20.72 P=0.001		F=22.56 P=0.001		

In this study, a statistically significant decrease in C.R.P levels and E.S.R levels were observed at the end of 2 months and 6 months in the vitamin A supplementation group than the control group.

In our study it was evident that there was a statistically significant improvement in the Karnofsky score in the study group when compared to the control group, at the end of 2 months and 6 months.

Table 3: Body mass index.

	Group				Independent t-test
	Control		Study		
	Mean	SD	Mean	SD	
BMI I	17.40	1.17	17.53	1.40	t=0.46 P=0.64
BMI II	17.83	1.21	18.50	1.24	t=2.60 P=0.01
BMI III	18.30	1.26	19.23	1.23	t=3.54 P=0.001
One way ANOVA F-test	F=6.22 P=0.003		F=19.33 P=0.001		

Table 4: Mid upper arm circumference.

	Group				Independent t-test
	Control		Study		
	Mean	SD	Mean	SD	
MUAC I	19.31	1.80	19.37	1.76	t=0.16 P=0.87
MUAC II	19.90	1.88	20.82	1.94	t=2.30 P=0.02
MUAC III	20.64	1.91	22.61	1.97	t=4.84 P=0.001
One way ANOVA F-test	F=5.75 P=0.001		F=33.84 P=0.001		

Table 5: C- reactive protein.

	Group				Independent t-test
	Control		Study		
	Mean	SD	Mean	SD	
CRP I	27.69	6.71	29.46	8.59	t=1.09 P=0.27
CRP II	19.44	6.33	14.74	5.54	t=3.77 P=0.001
CRP III	11.07	3.85	5.41	3.79	t=7.04 P=0.001
Oneway ANOVA F-test	F=95.38 P=0.001		F=99.34 P=0.001		

Nutritional status of the patients was assessed by body weight, body mass index and mid upper arm circumference. In our study it was observed that statistically significant improvement in B.M.I and M.U.A.C occurred in the study group and control group at the end of 2 months and 6 months. But the improvement was greater (10% from the baseline) in the study group when compared to the control group (5% from the baseline.

Table 6: Erythrocyte sedimentation rate.

	Group				Independent t-test
	Control		Study		
	Mean	SD	Mean	SD	
ESR I	37.07	13.06	37.72	15.69	t=0.21 P=0.83
ESR II	31.53	13.24	23.89	11.13	t=2.98 P=0.004
ESR III	22.36	10.67	17.24	6.14	t=2.81 P=0.006
One way ANOVA F-test	F=16.02 P=0.001		F=42.09 P=0.001		

DISCUSSION

This 8-week randomized, active controlled prospective study examined the beneficial effects of vitamin A supplementation at the dose of 25000 I.U. once weekly as an add on therapy with regular anti-tuberculosis treatment in patients with category I pulmonary tuberculosis. Anthropometric parameters, Karnofsky's clinical performance status score and biochemical parameters were assessed at the baseline and at the end of 2 months and 6 months. Clinically, the functional capability of the patient was assessed by Karnofsky clinical performance status score. It measured the improvement in the clinical outcome of the pulmonary tuberculosis patients. In our study it was evident that there was a statistically significant improvement in the Karnofsky score in the study group when compared to the control group, at the end of 2 months and 6 months. Nutritional status of the patients was assessed by body weight, body mass index and mid upper arm circumference. In our study it was observed that statistically significant improvement in B.M.I and M.U.A.C occurred in the study group and control group at the end of 2 months and 6 months. This was in correlation with the study carried out by Hanekom et al, which showed improvement of nutritional status with vitamin A therapy in childhood tuberculosis.[9]

C.R.P and E.S.R were mainly used as markers of inflammation. Measuring these values was useful in determining the disease progression or the effectiveness of treatment. Koyanagi A et al, had shown that higher C.R.P concentrations reflected stronger inflammatory response.[10] In this study, a statistically significant decrease in C.R.P levels and E.S.R levels were observed at the end of 2 months and 6 months in the vitamin A supplementation group than the control group. This could be due to the anti-oxidant effect of vitamin A. During pulmonary inflammation increased amounts of free radicals are produced, which cause disruption of the cell

structure and function. Vitamin A supplementation may limit free radical membrane damage during inflammation which protects cells from the damaging effects of free radicals.

The results of our study showed that administration of vitamin A as an add on therapy with regular anti-tuberculosis treatment had improved the quality of life in pulmonary tuberculosis patients. This is likely to be related to the immune modulating and anti-oxidant property of vitamin A. This is supported by the study carried out on experimental animal models, where vitamin A promoted differentiation and cytokine secretion of macrophages. Further vitamin A may also down regulate the secretion of pro-inflammatory cytokines e. g. TNF-alfa, IL-6 and modulate T-cell function.

CONCLUSION

This study shows that vitamin A as an add on therapy to the existing standard therapy improves the clinical response and decreases the disease activity to a greater extent than with routine standard drug therapy alone. Further research is needed in this area, especially focusing on greater levels of vitamins and micronutrients supplementation which may be necessary to overcome the oxidative stress and immunosuppression occurring in tuberculosis. Further the nutritional support could also contribute greatly to the restoration of physical function.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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