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Clinical efficacy of beta-sitosterol as adjuvant therapy for the treatment of tuberculosis in children

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Abstract

Introduction: Clinical investigations of childhood tuberculosis (TB) and treatment are challenged by the paucibacillary nature of the disease and serious side effects of standard anti-TB drugs. An adjuvant therapy may facilitate the efficacy and downgrade the occurrence of side effects associated with long-term therapy.

Objective: To investigate the efficacy of beta-sitosterol (BS) as adjuvant therapy to standard anti-TB drugs in children with TB.

Methods: Children in the age range of 6 to 18 years who were diagnosed with TB are enrolled in this randomised clinical study. Enrolled children were divided into two groups to receive either BS or placebo. Sputum and blood samples were collected after every month to assess the level of infection (Positive or negative) and evaluation of different blood related complications, respectively. Adverse events were evaluated in each patient and noted.

Results: BS adjuvant therapy resulted in an early negative test for TB as compared to placebo therapy. Significant difference was noted in the patients positive for TB test from month 3 to 6. Furthermore, the BS group showed greater improvements on radiological examination than the placebo group. Comparing the BS group to the placebo group, the BS group showed improvements in hemoglobin, haematocrit, neutrophil count, serum globulin, creatinine, and urea. The overall treatment completion rates were higher in the BS-therapy group than the placebo group with comparatively lower incidence for side effects such as hepatotoxicity.

Conclusion: Adjuvant BS with standard anti-TB drug therapy had the same impact on early infection mitigation and side effect incidence as standard therapy in children aged 6 to 12. to 18 years. Treatment completion was higher in the adjuvant group than the placebo group and was also safer.

Keywords: Tuberculosis, beta-sitosterol, adjuvant therapy, haematological parameters, completion rate

Introduction

Children under the age of 15 account for 10-15% of the 9 million cases of tuberculosis (TB) each year. Many of these cases are found in countries with high levels of TB ^[1]. Infection with Mycobacterium tuberculosis complex is estimated to affect one third of the world's population, but the extent of childhood TB is unknown. For reasons that are not fully understood, diagnosing TB is difficult because it is difficult to isolate the causative microorganism ^[2]. Children may present with a variety of symptoms of TB due to its rapid progression, potential spread to multiple organs and ability to mimic other infectious diseases ^[3]. A tuberculin skin test (TST) and abnormal chest X-ray are usually required to initiate treatment in low-incidence countries ^[3, 4]. It is recommended that patients take a combination of antibiotics for half a year or longer in order to treat tuberculosis. However, patients often discontinue treatment before they finish, increasing the likelihood of drug-resistant strains developing ^[5]. Many scientists believe mycobacteria can be so hard to kill because dormant cells exist even in affected patients and are more resistant to antibiotics than metabolically active bacteria.

As per World Health Organisation, children should be treated by pediatric TB specialists to prevent the spread of infectious TB disease, as well as children with immunodeficiency to treat when exposure to someone with infectious TB disease occurs. Taking the medications exactly as instructed by the doctor and finishing the medication are very important for children or anyone being treated for latent TB infection or TB disease. Standard therapy and compliance of patients can effectively cure adult patients, however very few studies are available in children. Despite this more than 25% TB patients eventually relapsed the infection and enters in the danger of drug-resistant TB.

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Among the key objectives of TB therapeutics is the discovery and development of new drugs that can enhance the treatment strategy, enhance safety, and address the infection as well as side effects [6]. Plant-based natural products are becoming increasingly important as phyto-drugs in the absence of effective therapeutic drugs to treat TB [7]. Studies on patients with pulmonary tuberculosis that were double-blind, randomized, placebo-controlled found that beta-sitosterol (BS) can significantly increase weight loss due to the disease [8]. According to the same study, patients receiving shad elevated lymphocyte, eosinophil, and monocyte counts. The detailed mechanism of this effect has not yet been studied. The efficiency of BS as an immune modulating agent in case of multi-drug-resistant tuberculosis needs further investigation.

Materials and Methods

Study design and Subjects

Children in the age range of 6 years to 18 years and who were diagnosed with pulmonary tuberculosis were identified. In the trial, children diagnosed with pulmonary tuberculosis based on sputum cultures or acid-fast bacilli microscopy were randomised to receive sitosterols or a placebo. The allocation of the patients to the different treatment groups was unknown to those conducting the trial. The beta-sitosterols and placebo were supplied as identical capsules. The active capsules contained 0.2 mg BS plus talcum and excipients, and the placebo capsules contained only 200 mg talcum. Patients received one capsule three times daily together with their standard TB therapy.

Clinical Evaluation

As part of a comprehensive evaluation, patients were evaluated upon admission and monthly by examining weight gain, radiological improvement, sputum culture, full blood count, differential white cell count, sedimentation rate, and liver function tests. After admission, a Mantoux test was performed with 5 units of purified protein derivative (PPD) (Japan) and monthly thereafter. The maximum period of involvement in the study was 4 months for patients to be included in the analysis of the final data. Patients with drug resistant tuberculosis were excluded from the analysis. Radiographs of the chest were evaluated independently by a physician and radiologist who were unaware of which treatment group each patient belonged to. The chest radiographs show indisputable improvements only after a considerable variation in radiological technique.

Results

Baseline demographic characteristics

In the present study, 40 children received beta-sitosterols versus 35 who were on placebo treatment. Three from the sitosterol and five from the placebo group were subsequently excluded as they could not complete the minimum duration of BS treatment (4 months). Two from each group died and one BS and 3 from the placebo group were found to be multidrug-resistant tuberculosis (resistance to isoniazid and rifampicin). The mean age of the 37 patients from the BS group was 12.6 years and that of the placebo group was 14.1 years (final n = 30). All these patients whose data is considered for the analysis were fully drug sensitive. The mean weight of the patients from the BS group was 22.6 ± 3.4 kg and that of the placebo group was

24.8 ± 2.8 kg.

M. tuberculosis isolated from their sputum each month of the treatment till 6 months and cultured to assess the infection. Number of patients positive for the MT test from both the groups at the end of each month of treatment is presented in table 1. In the BS treatment group 11 patients who were MT positive versus 13 in the placebo group at the end of the first month. Significant difference was noted in the patients positive for TB test from month 3 to 6 ($p < 0.05$).

Table 1: Number of patients with positive TB test

	Placebo (n = 30)	BS (n = 37)	P value
1 months	13	11	$p > 0.05$
2 months	12	9	$p > 0.05$
3 months	10	6	$p < 0.05$
4 months	8	4	$p < 0.05$
5 months	5	2	$p < 0.05$
6 months	2	0	$p < 0.05$

Similar to sputum test results, radiological assessment also showed improvement amongst the subjects in the BS group than the placebo group.

Blood samples were collected from each patient at different time points similar to sputum collection. Improvement in the haemoglobin, haematocrit, neutrophil count, serum globulin, creatinine and urea were seen in the BS group as compared to placebo group. Induration on Mantoux testing also did not differ between the two treatment groups. Weight gain was, however, significantly greater in the sitosterol group (mean gain 6.5 kg) than in the placebo group (mean gain 4.1 kg) ($P < 0.01$). Lymphocyte counts were higher in the sitosterol group ($P < 0.0001$), as were eosinophil counts ($P < 0.0001$). Significant group and time effects were also found for monocyte counts, platelet counts and sedimentation rate, but a significant interaction of group and time complicates the interpretation of the main effects.

The overall treatment completion rates were 91.5% in the BS-therapy group and 76.4% in the placebo group ($P < 0.01$). The rates of treatment discontinuation attributed to AEs were 1.3% in the BS-therapy group and 3.1% in the placebo group ($P < 0.05$). Placebo therapy subjects showed more side effects than the BS therapy group. Most common AEs in the BS-therapy or placebo group included 4 influenza-like events, 3 cutaneous events (all with pruritic rash and with oral blisters and fever), and 5 gastrointestinal tract events.

Table 2: Events of therapy non-completion and discontinuation

Variables	BS (n = 37)	Placebo (n = 30)
Non-completion, n (%)	3 (9.11)	7 (23.33)
Adverse drug reaction	2	4
Consent withdrawal	1	3
Poor adherence	0	1
Prevention not needed	0	1
Being afraid of side effects	1	1

Placebo participants had higher total bilirubin, AST and ALT levels than their placebo counterparts after 3 months of treatment. Overall, only three patients in the BS group had clinically relevant hepatotoxicity. On the other hand, 7 patients from the placebo group showed signs of clinically relevant hepatotoxicity.

Discussion

Adjuvant BS treatment along with the standard antituberculosis regimen showed better outcomes and was beneficial in the prevention of commonly observed side effects with standard therapies. BS therapy helps in weight gain, early negative test for TB and lower rate of hepatotoxicity events.

The majority of sputum cultures got negative by the end of 2 months of therapy and that radiological resolution of the majority of tuberculosis lesions occurred by the end of 6 months therapy. In both groups of patients, a considerable gain in weight occurred, but gain in weight was significantly greater in the sitosterol group. Number of patients with negative sputum were more in the BS group at all the time points than the placebo group. Similar results were observed in terms of radiological response to treatment.

There has been extensive research done on the haematological findings and treatment responses of pulmonary tuberculosis patients. We have evaluated various blood parameters to evaluate the causal relationship of anti-TB drugs with the occurrence of anemia, lymphopenia, neutrophil leucocytosis, monocytosis, eosinopenia and thrombocytosis. The institution of appropriate chemotherapy will usually lead to a resolution of the anaemia, a rise in the lymphocyte count, a fall in the polymorphonuclear leukocyte count, a fall in the polymorphonuclear leukocyte count and the monocyte count, a rise in the eosinophil count and a fall in the platelet count. Our patients experienced this pattern of events; however, it should be noted that there was a significant increase in lymphocytes and eosinophils in those taking sitosterols as compared to placebo receiving subjects. This suggests that the improvement in the blood parameters may prevent the serious side effects when BS was concomitantly provided with standard anti-TB therapy.

Overall completion rate of the treatment was more in the BS group. This may contribute to the lesser evidence of side effects and positive effects of the therapy. Several significant differences were found between those individuals who were given sitosterols and those who were not, in a double-blind randomized placebo-controlled trial of patients with pulmonary tuberculosis. Weight gain, peripheral blood lymphocyte and eosinophil counts, and weight gain were both improved in sitosterol-treated patients. Despite the possibility that these differences are merely accident findings, the results could be cautiously interpreted as indicating that beta-sitosterols may have a beneficial effect.

Conclusion

Children receiving beta-sitosterol in addition to an effective antituberculosis regimen experienced substantial weight gain and higher lymphocyte and eosinophil counts. The effects of beta-sitosterols on tuberculosis patients and patients with similar immunopathologies must now be studied in a larger number of patients.

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