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Original Article

Effect of Low-Dose Steroids as an Adjunct to Anti-Tubercular Therapy on Lymph Node Regression in Tuberculous Lymphadenitis: A Randomized Controlled Trial

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ABSTRACT

Objective: To study the effect of low-dose steroids in addition to anti-tubercular treatment on the regression of Lymph node size in patients with Tuberculous Lymphadenitis

Study Design: Randomised Control Trial (NCT06236152).

Place and Duration of Study: Department of Medicine, Pak Emirates Military Hospital, Rawalpindi, Pakistan, from Sep 22 to Dec 23.

Methodology: Patients with Tuberculous Lymphadenitis who presented to PEMH Rawalpindi were randomized into two groups of 55 patients each. Group-A was given low-dose steroids with ATT, and Group-B was given a placebo with ATT. Lymph node (LN) size was measured at start of treatment and followed up after 2 months and end of treatment. LN size regression was noted and compared in both groups along with incidence of side effects of steroids and ATT drugs.

Results: The largest reported lymph node or the matted nodal mass size, before the start of the treatment was 4.09 ± 1.41 cm and 3.98 ± 1.26 cm in Group-A and Group-B respectively. In Group-A, 20 (36.4%) patients achieved regression in the lymph node size by 50% at the end of consolidation phase, whereas in Group-B 18 (32.7%) achieved the same (p=0.430). By the end of 6 months of treatment, 38 (69.1%) patients of Group-A had achieved regression in the lymph node size of more than 50% while 35 (63.6%) of the Group-B patients had achieved the same (p=0.235).

Conclusion: A lower dose of prednisolone was of limited benefit and ineffective for regression of lymph node size as compared to alone standard ATT.

Keywords: ATT, Lymph node, Prednisone, Steroids, Tuberculosis, Tuberculous lymphadenitis.

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INTRODUCTION

Tuberculosis's earliest records date back to the origin of civilisation itself, and yet it remains one of the most elusive of the diseases, haunting the human population in the third world.[1] Newer drugs and treatment protocols remain a major focus of discussion in academic circles. Pulmonary tuberculosis is the most common form of the disease, making up to 80 percent of the cases.[2] The most common form of extrapulmonary tuberculosis is the tuberculous lymphadenitis or Scrofula, presenting as cervical lymphadenopathy most of the time. Tuberculous lymphadenitis progresses through lymph node enlargement, showing reactive hyperplasia, adherence to the surrounding tissues, central caseation, and cold abscess formation, and ultimately a draining sinus.[3] Confirmation of diagnosis can only be achieved by demonstration of the mycobacterial DNA in the nucleic acid amplification tests (NAATs), visualization of the Acid Fast Bacilli, or mycobacterial culture; however, for countries like Pakistan, where TB is rampant, presence of granulomatous inflammation with caseating necrosis, pathognomonic sign of TB, in a lymph node biopsy is highly suggestive of tuberculosis.[4]

Treatment of Tuberculous lymphadenitis comprises of standard 1st line 4 drug regimen for 6 months, comprising of Isoniazid, Rifampicin, Ethambutol and Pyrazinamide for the first 2 months followed by Isoniazid and Rifampicin for the next 4 months.[5] Response to the treatment is slower as compared to pulmonary tuberculosis and patients frequently complain of persistent pain and swelling along with paradoxical lymph node enlargement as well at times. Steroids play a pivotal role in limiting the long term damage in cases of tuberculous pericarditis, meningitis and pleural effusion.[6] Addition of steroids to the anti TB treatment in cases of tuberculous lymphadenitis has been tried in some small scale studies but is currently not recommended in the guidelines.[7]

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Pakistan accounts for up to 60% of the cases of TB in the Eastern Mediterranean region of the World Health Organization (WHO), with an overall prevalence of 376 cases per 100,000 population.[8] As of November 2020, Tuberculosis has been declared a mandatory notifiable disease in Pakistan by the Health Department of Government of Pakistan.[9] A few of the notorious factors which contribute to its spread include low socioeconomic status, poor hygiene, overcrowding, immunosuppression due to HIV infection (human immunodeficiency virus), diabetes, and an inadequate social awareness regarding disease prevention and treatment.[10]

With such a high prevalence of the disease, it becomes punitive that robust TB control programs are run with an aim of not only rooting out the problem but also scientifically studying it so as to add useful information to the current literature available on the disease. This randomised control trial was started with this very idea of studying the role of low dose steroids with standard anti TB drugs during the consolidation phase of treatment for tuberculous lymphadenitis. Some International studies have reported an early resolution of lymphadenopathy when treated with 1mg/kg of prednisolone per day for initial 4 weeks of treatment, but this much dose of steroids causes a number of complications. Our trial will look into the use of a low dose of steroids so as to avoid any of the side effects of the treatment.

METHODOLOGY

The study was conducted as a single blinded Randomised Control Trial at Pak Emirates Military Hospital, Rawalpindi Pakistan, from Sept 22 to Dec 23 over a period of 16 months. A written informed consent was obtained from all the participants prior to the study, an approval was sought from the Hospital Ethical Review Board (ERB #A/28/EC/390/2022), and study was registered in Registry of Clinical Trials (NCT06236152). Sample size was calculated by WHO sample size calculator taking confidence interval 95%, margin of error 5% using formula for hypothesis testing for use of low dose steroids in two population proportions as used in reference study (RCT) by Bunkar *et al*.[11] The estimated sample size came out to be 108.

Inclusion Criteria: Patients of either gender with age 15-60 years, presenting with newly diagnosed tuberculous lymphadenitis during study period were included in the trial.

Exclusion Criteria: Patients who have concurrent HIV infection and tuberculosis of any other organ, tuberculous lymphadenopathy in the abdomen or mediastinum or previously treated tuberculosis of any site, malignancy, and immunocompromised patients were excluded.

Patients who presented to the medical outpatient department with complain of symptoms and signs suggestive of extra pulmonary (Lymph node) tuberculosis were thoroughly examined and then investigated with a complete baseline investigations panel (including Chest X-ray), Mantoux test, Imaging via ultrasonography and HIV screening. A lymph node fine needle aspirate was obtained initially whenever possible and was sent for acid fast staining, NAAT (GeneXpert for MTB DNA), Mycobacterial culture and cytology. An excisional biopsy was done later on for diagnosis if required. Pathognomonic findings of granulomatous inflammation and caseating necrosis on the histopathological analysis was also considered a confirmation of tuberculosis keeping in view the high prevalence of the disease in the country and a reported accuracy rate of 95%.[12] Patients were divided into two groups A and B via lottery method and a single blind protocol was ensured. Largest lymph node or size of the matted lymph node mass was recorded in 2 dimensions by using measurements made by ultrasonography prior to start of treatment. Group-A was started on the standard, weight adjusted anti TB treatment comprising of Tablet Myrin-P forteR (Isoniazid 75mg, Rifampicin 150mg, Ethambutol 275mg, Pyrazinamide 400mg) and Tablet Pyridoxine 50mg per day along with Tablet Prednisolone at a dose of 10mg per day for the initial 2 months. Group-B was started on Tablet Myrin-P forteR and Tablet Pyridoxine 50mg per day along with a placebo. Treatment was switched to weight adjusted Tab RifinahR (Isoniazid 150mg, Rifampicin 300mg) and Tablet Pyridoxine 50mg per day at the end of consolidation phase and steroids / placebo were discontinued. Monthly follow up was advised to both groups (Figure). A regression in lymph node size of more than or equal to 50% of the initial measurements was considered significant. Size measurements were taken at each follow using ultrasonography as before along with improvement in the symptoms and weight of the patient on a monthly basis. Treatment complications were also noted for both groups. Failure to gain weight and continuing symptoms of tuberculosis at 5 months of treatment were considered failure of the treatment.

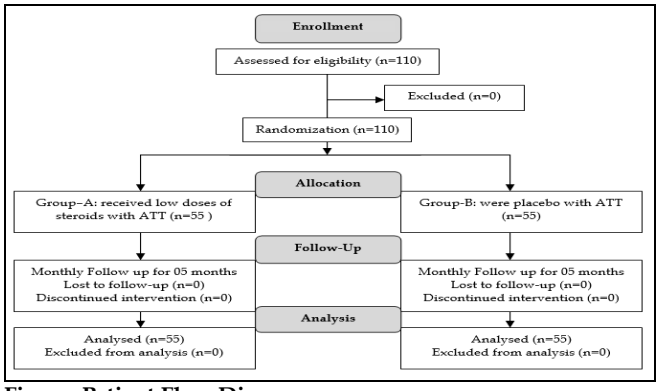

Figure: Patient Flow Diagram

Primary outcome was to observe a significant change in the lymph node size at the end of consolidation phase and at the end of treatment as well as weight gain at the same temporal junctures. Secondary outcome was focused on the incidence of cold abscess formation and reported adverse effects of standard ATT or prednisolone.

Data were entered in the Statistical Package of Social Sciences software version 25.00 (SPSSv25) and were analysed. A 2 x 2 table was made for the response to treatment i.e. lymph node size regression between the groups and relative risk was calculated. The significance was checked using Pearson Chi Square test of significance for qualitative variables. For comparison of quantitative variables the groups, independent samples T test was applied and a *p*-value ≤0.05 was considered significant.

RESULTS

One hundred and ten (110) patients were included in our trial after division in to two equal groups. Group-A (ATT + Prednisolone) included patients with a mean age of 41.67±9.85 years with 32(58.2%) males and 23(41.8%) females as compared to Group-B (ATT + Placebo) in which patients had mean age of 42.20±9.91years with 30(54.5%) males and 25(45.5%) females (*p*=0.988). The largest reported lymph node or the matted nodal mass size, before the start of the treatment was 4.09±1.41 cm and 3.98±1.26 cm in Group-A and Group-B respectively. The mean weight of 49.45±8.19 kg and 50.84±7.05 kg was noted prior to start of treatment in Group-A and Group-B respectively (*p*=0.309). At the end of treatment, Group-A had mean weight of 56.44±7.29kg (mean weight gain 6.99kg) and Group-B had mean weight of 57.71±5.82 (mean weight gain 6.87kg) (*p*=0.058) (Table-I).

Group-A patients had a mean fasting blood sugar of 101.71±11.01 mg/dL at the end of consolidation phase whereas Group-B patients had a mean fasting blood sugar of 96.76±9.86 mg/dL at the same temporal juncture (*p*=0.109) (Table-I).

Table-I: Comparison of Studied Variables in Both Groups (n=110)

Parameter		Group-A (ATT* + Prednisolone) n=55	Group-B (ATT + Placebo) n=55	*p*-value
Age	(mean years± SD)	41.67±9.85	42.20±9.91	0.988
Gender	Male, n(%)	32(58.2%)	30(54.5%)	0.464
	Female, n(%)	23(41.8%)	25(45.5%)	
Weight	At 0 month (mean kg±SD)	49.45±8.20	50.84±7.05	0.309
	At 6th month (mean kg±SD)	56.44±7.29	57.71±5.82	0.058
BSF*	(mean mg/dL± SD)	101.71±11.01	96.76±9.86	0.109

**ATT: Anti-Tuberculous Treatment, BSF: Blood Sugar Fasting, SD: Standard Deviation*

In Group-A, 20(36.4%) patients achieved regression in the lymph node size by 50% at the end of consolidation phase, whereas in Group-B 18(32.7%) achieved the same (*p*=0.430). By the end of 6 months of treatment, 38(69.1%) patients of Group-A had achieved regression in the lymph node size of more than 50% while 35(63.6%) of the Group-B patients had achieved the same (*p*=0.235) (Table-II).

Table-II: Regression of Lymph Node Size compared between Experimental and Control Groups (n=110)

Timeline	Group-A (ATT* + Prednisolone) n=55	Group-B (ATT + Placebo) n=55	*p*-value
2 Months	20(36.4%)	18(32.7%)	0.430
6 Months	38(69.1%)	35(63.6%)	0.235

**ATT: Anti-Tuberculous Treatment*

As far as the adverse drug reactions reported by either of the groups is concerned, 36(32.7%) patients from both groups did not report any. Major adverse drug reaction reported by 37(33.6%) from both experimental and control groups was dyspepsia. Other adverse drug reactions reported by either of the groups summarized in the table-III.

Table-III: Comparison of Adverse Effects in Experimental versus Control Group (n=110)

Adverse Reaction	Group-A (ATT* + Prednisolone) n=55	Group-B (ATT + Placebo) n=55	*p*-value
None, n(%)	21(38.2%)	15(27.3%)	0.462
Dyspepsia, n(%)	20(36.4%)	17(30.9%)	
Pain in Lymph Node, n(%)	5(9.1%)	6(10.9%)	
Abscess Formation, n(%)	4(7.3%)	5(9.1%)	
DILI*, n(%)	2(3.6%)	5(9.1%)	
Treatment Failure, n(%)	3(5.5%)	7(12.7%)	

**ATT: Anti-Tuberculous Treatment, DILI: Drug-Induced Liver Injury*

DISCUSSION

This randomized controlled trial was carried out to find out if there is any benefit of adding low-dose steroids to the standard first-line anti-tuberculous regimen. Although a huge number of tuberculosis cases routinely visit the healthcare setups, the limited focus of the study was on a specific set of Tuberculosis cases, i.e. those with tuberculous lymphadenitis. Due to the overlapping evidence base, we tried a middle ground and went for addition of a low dose of steroids to the standard ATT regimen to avoid the potential adverse effects; however, no significance of this regimen was found. The resolution of lymphadenopathy and clinical improvement were comparable in both groups. The side effect profile was also comparable in both experimental and control groups.

It goes without saying that tuberculosis is rampant in our part of the world, largely attributable to the unchecked population growth, lesser living space per person, and lack of a robust healthcare system.[13] A similar Randomized Controlled trial was conducted by Bunkar *et al.,* who compared two groups of patients with tuberculous cervical lymphadenopathy. The experimental group received 1mg/kg per day of prednisolone for the initial 4 weeks. Steroid usage hastened the clinical recovery, but gastrointestinal side effects were significant in the experimental group.[11] Sharmin *et al.,* also reported a complete resolution of lymphadenopathy in the experimental group, far more than the control.[14] However, it is pertinent to note that both trials used a Prednisolone dose of 1 mg/kg body weight, whereas this clinical trial used 0.5 mg/kg.

Tuberculosis results in tissue damage via a Type 4 hypersensitivity reaction.[6] A transient, paradoxical worsening of the cervical lymphadenopathy after starting ATT has been described in a study by Chahed *et al.,* and has been known to respond well to steroids, indicating that steroids may have a beneficial role here as well.[15] Amin *et al.,* have reviewed and shed light on the literature of steroid use in tuberculosis. There is conflicting evidence, and both schools of thought exist. The clinical arguments are countered by the mechanisms of action of steroids, where they inhibit the pathways of immune response against Mycobacterium.[16]

Djochie *et al.,* have reported that dyspepsia is the most common side effect of anti-tuberculous drugs similar to findings of this trial, followed by nervous system and skin reactions, which was not observe at all.[17] In a cross-sectional study by Sankar *et al.,* some degree of hepatotoxicity is seen in around 1/3rd of the patients receiving anti-TB drugs, but fewer have raised hepatic enzymes that need stopping the drugs. In our study, we observed in less than 10% of the cases, but none needed to stop the anti-TB drugs.[18]

Schutz *et al.,* reported that significant improvement in terms of regression in lymph node size and weight recovery was observed in 67.2% of ATT + prednisone Group-And 45.7% in ATT + placebo group (p<0.005.[19] Gupta *et al.,* studied the role of steroids (1mg/kg) in regression of lymph node size and complete resolution of lymph nodes were seen in 57(96%) patients who received steroids along with ATT drugs in comparison to 40(66.7%) patients who received placebo (p<0.01).[20]

LIMITATION OF STUDY

The most significant limitation is the small sample size. Additionally, the study was conducted within a single healthcare setup that serves a specific clientele. Large-scale randomized controlled trials are necessary, but not at the expense of causing harm to patients, which presents a dilemma for this disease—an ailment that still reveals new insights despite its age. Furthermore, the role of low-dose steroids needs to be examined with a larger sample size in a multi-center study before applying the results to the general population.

CONCLUSION

Use of a lower dose of steroids for improving the recovery in tuberculous lymphadenitis patients is of limited benefit. A higher dose of steroids has been advocated to be beneficial for hastening the regression of cervical lymph nodes; however, it has never been made part of the guidelines because of less evidence available.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

FJA & SAS: Data acquisition, data analysis, critical review, approval of the final version to be published.

AB & MUU: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

HAS, FZ & MH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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