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Adjunct Prednisolone Versus Anti Tuberculous Drugs Alone for Treatment of Tuberculous Pleurisy

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ABSTRACT

To determine the effect of adjunct prednisolone therapy, a randomized controlled trial was conducted involving 46 hospitalized patients having biopsy proven tuberculous pleurisy and were followed till the end of treatment. Patients were divided into two groups; one group was treated with standard anti tuberculous treatment while the other (group 2) was assigned adjunct prednisolone with anti tuberculous drugs. Fever and constitutional symptoms disappeared faster in group 2 (*P value* <0.001). After one month, there was a significantly greater reduction in the size of pleural effusion in group receiving adjunct prednisolone, but after 4 and 8 months the difference was not statistically significant. It was concluded that adjunct prednisolone alleviates symptoms and effusion earlier than anti tuberculous drugs alone but does not reduce the development of pleural thickening.

Key words: Corticosteroids, pleural effusion, prednisolone, tuberculosis.

INTRODUCTION

Tuberculosis is one of the major causes of pleural effusion in many countries including Pakistan.[1,2] Pleural tuberculosis is the second most common extraparenchymal manifestation of pulmonary tuberculosis after lymphatic tuberculosis.[3] The traditional explanation for the development of tuberculous pleurisy is that a small tuberculous subpleural focus ruptures into the pleural space, setting up an interaction between the TB bacilli or its antigens and the $CD4^+$ T lymphocytes. The clinical syndrome is a reflection of an in situ delayed hypersensitivity reaction in which plasma proteins exude into the pleural space and $CD4^+$ helper T cells accumulate, proliferate, and cause production and release of inflammatory mediators.[4] Tuberculous pleurisy is most often due to reactivation disease in adults and to primary tuberculous infection in children.[5] The disease usually presents as an acute febrile illness causing a nonproductive cough (94%) and pleuritic chest pain (78%) without an elevation in the peripheral white blood cell count while the non specific constitutional symptoms include pyrexia, night sweats, chills, weakness, anorexia and weight loss.[6]

The typical fluid in tuberculous pleural effusion is straw-colored exudate having protein concentration between 3.0 to 5.0 g/dL and elevated LDH level in approximately 75%, with levels commonly exceeding 500 IU/L.[7] Tuberculous pleural effusions are unilateral in almost all cases, are small to moderate in size and occur slightly more often on the right.[7] Pleural fluid cultures are positive in less than 30% and cultures obtained from pleural biopsies are positive in 40 to 80% of cases.[8] Pleural tissue can be obtained via thoracoscopy or closed, percutaneous needle biopsy. The two methods are believed to have comparable sensitivities, and the latter is generally preferred in areas where tuberculous pleuritis is common.[9,10] The initial therapy of tuberculous pleural effusion usually includes four standard anti tuberculous agents: isoniazid, rifampin, pyrazinamide, and ethambutol. With therapy, most patients become afebrile within two weeks, and pleural fluid is resorbed within six weeks. However, some patients take up to eight weeks to defervesce, and fluid resorption may take up long time usually up to four months.

There has not been a study in our hospital addressing use of adjunct steroids and most of the studies already done have controversial results for steroids use in tuberculous pleural effusion. It has been shown in selected patients; the administration of corticosteroids can shorten the duration of fever and time to resolution of fluid, although the precise risks and benefits of corticosteroids in this setting are debatable.[11] There are 50% chances of development of pleural thickening following pleural tuberculosis.[12]

The aim of the study was to evaluate the role of adjunct prednisolone in comparison to anti tuberculous drugs alone in context to various end points including improvement in clinical symptoms, resolution of pleural effusion and residual pleural thickening.

MATERIAL & METHODS

It was an open label randomized controlled trial from February 2008 to December 2009 that included 32 adult males and 14 females between 18 to 42 years of age having almost same sized biopsy confirmed exudative lymphocytic/neutrophilic tuberculous pleural effusions. The study was conducted at pulmonology ward, Shaikh Zayed Hospital, Lahore enrolling 46 available patients by convenient sampling. The exclusion criteria included those with loculated pleural effusions, hemorrhagic or pyemic effusions, diabetes mellitus and other co-morbid conditions like severe renal, hepatic, cardiac or neurological disease.

After explaining the nature of study and obtaining informed consent, the recorded parameters included age, gender, weight, address and phone number. Non specific constitutional symptoms including fever, night sweats, fatiguability and anorexia etc as well as respiratory symptoms including cough, sputum production, chest pain, dyspnoea, wheeze and hemoptysis were recorded. Baseline chest radiograph was taken and the size of pleural effusion was estimated according to the area of opacification caused by the pleural fluid on the chest radiograph. Opacified hemithorax of ≥ two thirds of the hemithorax was classified as large effusion; involvement of > one third of the hemithorax but < two thirds was considered medium; if it involved ≤ one third of the hemithorax, it was considered small grade pleural effusion.

Patients were allocated to two treatment groups, one received standard anti tuberculous drugs alone (n=23) and the other group received standard anti tuberculous drugs along with prednisolone 30 mg/day for 4 weeks with tapering in next 2 weeks (n=23). One of the family members was assigned the job of directly observing the patient swallowing the tablets to ensure compliance.

All patients were followed in the outpatient department at one, four and eight months of treatment. Patients were given telephonic access and were also allowed to contact directly in ward in case of any drug related adverse event or other query. Their clinical symptoms were re-analyzed at follow up visits and record for weight change was maintained with change in anti tuberculous drug dosages according to weight categorization. Chest x-rays were also repeated at one, four and eight months of treatment follow ups and compared with the baseline radiograph.

Reduction in pleural effusion was considered to be 50% if the amount of fluid decreased to a lower grade or 25% if there was reduction in the amount of fluid but still within the same grade. The size of residual pleural thickening (scarring) was estimated using the same measurement grades as pleural effusion (severe ≥ two thirds of the hemithorax, moderate > one third but < two thirds, and mild ≤ one third). The term "obliteration of costophrenic angle" was used when the angle was > 90º. Ultrasound of the chest was performed at the end of treatment to confirm the presence of pleural thickening seen on chest radiograph.

For statistical analysis, the chi-squared test was used as appropriate. P *value* < 0.05 was considered significant.

RESULTS

Among 46 hospitalized patients, there were 32 males and 14 females (8 in group A and 6 in group B). Three patients in group A receiving anti tuberculous drugs alone and two patients in second group receiving adjunct prednisolone and anti tuberculous drugs had drug related adverse effects

(gastritis, hepatitis and joint pains) which were managed but the patients were lost to follow up. The remaining 41 patients completed the study. There were no significant differences between the two groups regarding age, sex or clinical symptoms. The average time of disappearance of fever and constitutional symptoms (night sweats, fatiguability and anorexia) in the group who were treated with adjunct corticosteroids was 7±2.2 days compared to 18±1.8 days in the other group (*P value* <0.001). Two patients, 1 in the corticosteroid group and the other in group 1, showed paradoxical response to anti tuberculous treatment with increase in fever and size of pleural effusion that lasted for 5 weeks. There were no differences between the two treatment groups with regard to resolution of pleural effusion or extent of pleural thickening. After one month, there was > 50% reduction in the size of pleural effusion in the group having adjunct corticosteroid treatment (group 2) compared with 25% in the (group 1) receiving anti tuberculous drugs alone. In both groups, there was progressive reduction of size of pleural effusion up to the fourth month of treatment. After 8 months there was, however, no statistically significant difference among the 2 groups. No significant relation was found between size of effusion and later pleural scarring as appreciated on follow up chest radiographs and ultrasound examination of the chest with p-value 0.145 (Table 1).

Table 1: Comparison of size of pleural effusion at presentation and residual pleural thickening after 8 months treatment.

Pleural thickening	Pleural effusion			Total
	Small	Medium	Large	
Severe [a]	-	1	2	**3**
Moderate [b]	-	2	1	**3**
Mild [c]	3	4	3	**10**
Obliteration of costophrenic angle	7	3	5	**15**
Normal chest radiograph	7	2	1	**10**
Total	**17**	**12**	**12**	**41**

Chi-square = 12.14 P-value = 0.145

[a]Severe: ≥ 2/3 of the hemithorax;[b] moderate: > 1/3 but < 2/3;[c]mild: ≤ 1/3.

DISCUSSION

The possibility of tuberculous pleurisy should be considered in every patient with an undiagnosed pleural effusion, for if this diagnosis is not made the patient will recover only to have a high likelihood of subsequently developing pulmonary or extrapulmonary tuberculosis.[13] Corticosteroids are often prescribed as an adjunct in the treatment of various forms of tuberculosis (TB) and for the prevention of complications, such as constrictive pericarditis, hydrocephalus, focal neurological deficits, and sometimes in intestinal strictures but their role in tuberculous pleurisy has been controversial.[14,15] Adjunctive corticosteroids therapy appears to offer significant short-term, but minimal long-term, benefit for patients with TB.[16]

In this present study, corticosteroids hastened the recovery of constitutional symptoms and led to early reduction in symptoms, but after 4 and 8 months there was no difference between the groups. Some researchers are of the opinion that, although benefit has been shown in pleural disease, adjunct prednisolone therapy is not routinely recommended unless there are significant systemic symptoms of pyrexia or a particularly large effusion.

One of the common sequelae of pleural TB is residual pleural thickening, which may be seen in half of patients with the disease. Neither patient clinical characteristics nor pleural fluid biochemistry and cytology are predictive of the ultimate development of pleural scarring/thickening, and neither corticosteroid therapy nor repeated pleural fluid aspiration aid preventing this complication.[12] Though corticosteroids may bring about more rapid resolution of pleural effusion with less pleural scarring, scarring only rarely presents a problem in any event.[16]

Similar findings were reported previously as were found in this study.[6, 11, 16] There were some limitations in this study that are worth mentioning. There may have been selection bias for the two groups, since there was no real randomization and the groups were divided according to the time they presented. The sample size was small because of no isolated TB ward in our hospital and the major burden of patients with tuberculosis is diverted to other TB clinics in the town to other hospitals. The

duration and dose of prednisolone treatment could have been reduced and compared to another treatment group.

CONCLUSION

The use of adjunct prednisolone in addition to standard anti tuberculous drugs has no effect on residual pleural thickening but does help in shortening the duration of fever and time to resolution of pleural effusion. It is therefore recommended that prednisolone should be added to anti tuberculous treatment in selected individuals experiencing more symptoms and those with larger pleural effusions.

REFERRENCES

1. Khan FY, Alsamawi M, Yasin M, Ibrahim AS, Hamza M, Lingawi M, et al. Etiology of pleural effusion among adults in the state of Qatar: a l-year hospital-based study. East Mediterr Health J. 2011;17:611-8.
2. Khurram M, Jaffery AH, Khar HTB, M Farooq Malik MF, Burki UF et al. Evaluation of Lymphocytic Exudative Pleural Effusion with Pleural Biopsy J Coll Physicians Surg Pak 2002;12:74-7.
3. Rieder HL, Snider DE Jr, Cauthen GM. Extrapulmonary tuberculosis in the United States. Am Rev Respir Dis 1990; 141:347-51.
4. Ellner JJ, Barnes PF, Wallis RS, et al. The immunology of tuberculous pleurisy. Semin Respir Infect 1988;3:335-42.
5. Merino JM, Carpintero I, Alvarez T, Rodrigo J, Sanchez J, Coello JM. Tuberculous pleural effusion in children. Chest, 1999;115:26.
6. Berger HW, Mejia E. Tuberculous pleurisy. Chest 1973; 63:88.
7. Valdes L, Alvarez D, San Jose E, Penela P, Valle JM, García-Pazos JM, et al. Tuberculous pleurisy: a study of 254 patients. Arch Intern Med. 1998;158:2017.
8. Diacon AH, Van de Wal BW, Wyser C, Smedema JP, Bezuidenhout J, Bolliger CT et al. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J, 2003;22:589.
9. Toloba Y, Diallo S, Sissoko BF, Kamate B, Ouattara K, Soumare D et al. Pleural puncture biopsy in the aetiological diagnosis of pleurisy. Rev Mal Respir. 2011;28:881-4.
10. Ashraf S, Ashraf A, Asif SA. The role of closed needle biopsy of the Pleura in exudative Pleural Effusion. Pak J Chest Med, 2003;9:11-6.
11. Matchaba PT, Volmink J. Steroids for treating tuberculous pleurisy. Cochrane Database Syst Rev. 2000.
12. Barbas CS, Cukier A, de Varvalho CR, Barbas Filho JV, Light W. The relationship between pleural fluid findings and the development of pleural thickening in patients with pleural tuberculosis. Chest. 1991; 100:1264-67.
13. Light RW. Update on tuberculous pleural effusion. Respirology. 2010;15:451-8.
14. Kadhiravan T, Deepanjali S. Role of corticosteroids in the treatment of tuberculosis: an evidence-based update. Indian J Chest Dis Allied Sci. 2010;52:153-8.
15. Engel ME, Matchaba PT, Volmink J. Corticosteroids for tuberculous pleurisy. Cochrane Database Syst Rev. 2007.17:CD001876.
16. Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroids therapy for tuberculosis: a critical reappraisal of the literature. Clin Infect Dis, 1997; 25:872–87.

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