Role of corticosteroid as an adjunct to antitubercular drugs in the treatment of pleural effusion: A one year study

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Abstract

Background: To compare the effect of corticosteroid as an adjuvant to antitubercular treatment (ATT) in view of improving the symptoms, resolution of pleural fluid and prevention of pleural thickening.

A prospective case control study was conducted in the Department of Respiratory Medicine, King George’s Medical University, Lucknow, India.

Methodology: The present study has been conducted on 76 diagnosed cases of tubercular pleural effusion, 38 in case group and 38 in the control group. ATT was given to both the groups and steroid (prednisolone) was given to the case group as an adjuvant to ATT. Clinico-radiological follow-up has been done at the end of 1st, 2nd, 4th, and 6th month.

Results: The mean duration of resolution of fever, cough and breathlessness in case group was significantly less as compared to control group and their differences were statistically significant with p value < 0.05. The mean duration of resolution of chest pain in case group was less but not statistically significant. It was also observed that the rate of resolution of effusion was significantly higher in case group as compared to control group up to the end of 2nd month of treatment, after that the difference was not significant. At the end of 6th month, 35 patients developed pleural thickening, out of which 21 were of the control group while the remaining 14 were of the case group.

Conclusions: Use of corticosteroids as adjuvant to ATT resolve the clinical symptoms more quickly and hasten the absorption of pleural fluid and to some extent pleural thickening in patients with tubercular pleural effusion.

Introduction

Tuberculosis is a major health problem in a developing nation like India. It can involve any organ system of body and is broadly categorized as Pulmonary Tuberculosis & Extrapulmonary TB. Extrapulmonary tuberculosis constitute about 20 per cent of all cases of TB [1,2]. In HIV-positive patients, Extrapulmonary TB accounts for more than half of all cases of TB [3,4]. Pleura followed by the lymphatic system is the most common extrapulmonary site of tubercular infection. Tubercular effusion is caused by release of Mycobacterium tuberculosis bacteria due to rupture of a parenchymal caseous lesion adjacent to pleura leading to excessive pleural fluid formation than its removal [5].

Type IV hypersensitivity reaction i.e. Delayed type, to these caseous tubercle material is responsible for most clinical features of pleural effusion caused by tuberculosis. Apart from inflammation it also can cause significant tissue damage in form of fibrosis which is a well described complication of tuberculosis pleuritis with a prevalence ranging from 5% to 55% [6,7]. Few studies show long term deleterious sequel of pleural fibrosis leading to pleural thickening and observed that more than one centimetre pleural thickening was frequent in patients with breathlessness, deranged spirometric findings and chest pain [8].

The gold standard diagnostic test for tubercular pleuritis is detection of Mycobacterium tuberculosis bacteria by culture and microscopy. The presence of granulomas with caseous necrosis in the pleural biopsy and acid fast bacilli in Zeel-Neelsen staining done on histopathological examination is also confirmative of tuberculosis [9-11].

However, in areas with high prevalence of tuberculosis the diagnosis can be made on the basis of high cell lymphocyte and high ADA levels. Thus, the diagnostic importance of ADA depends on the prevalence of tuberculosis in that area also. [12,13]. The cases with non-diagnostic lower level of ADA shall require alternative diagnostic tests like pleural biopsy for histopathology. So, while interpreting ADA levels of a patient one must keep in mind the clinical correlation.

Although antitubercular treatment (ATT) provided to the patients is effective still this notorious disease leads to
unwanted sequels of pleural thickening and fibrosis. Adjuvant use of steroid with ATT has always been a subject of interest for researchers and pulmonologists and several studies has been done showing the benefits of adding steroid to the antitubercular drugs as an adjuvant [14-16].

This is due to capability of steroids to subdue all types of hypersensitivity reactions including Delayed type hypersensitivitiy. In this study we studied the adjuvant effect of corticosteroids when given along with ATT in reducing the fibrotic sequel and accelerating the resolution of pleural effusion as well as the clinical symptoms.

Materials and Methods
The present work is a one year prospective case control interventional study done at a tertiary care centre to see the effects of corticosteroid as an adjuvant to ATT in the improvement of symptoms, resolution of pleural fluid, and decrease in pleural fibrosis complication in the tubercular effusion patients. Ethical approval was obtained from the ethical committee of the institution. Written informed consent from the study subjects was obtained. A total 76 newly diagnosed patients of tubercular pleural effusion were included in our study, 38 patients in case as well as control group each. The diagnosis of tubercular pleural effusion was based on microbiological and biochemical examination of pleural fluid including ADA level (> 40 IU/L) [17]. Other possible causes of pleural effusion such as pneumonia, carcinoma, congestive cardiac failure and others were excluded through relevant diagnostic investigations. Patients with history of steroid-related adverse event, pepsic ulcer disease, psychiatric illness, hepatic diseases, renal diseases, diabetic patients, autoimmune disorder, HIV seropositivity, alcoholism, pregnancy, massive pleural effusion, bilateral pleural effusion, parenchymal involvement (radiologically or microbiologically proven), and atypical pleural effusion were excluded from the study. Massive pleural effusion cases were excluded as they are not clinically stable for a thesis study and are undergone therapeutic tapping thus were considered beyond the scope of our study. Those who were eligible for the study were randomly assigned to treatment with prednisolone added to antitubercular treatment (case group) or with antitubercular treatment only (control group). The antitubercular treatment includes directly observed treatment, short-course (DOTS) regimen for a duration of six months. Prednisolone was administered in an oral dose of 1 mg/kg/day for first fortnight, and then gradually tapered dose of 0.5 mg/kg/day for next five days of treatment, then to 0.25 mg/kg/day for later five days, and finally to 0.10 mg/kg/day for the remaining days of the first month of medication.

Evaluation was done in form of history, physical examination, Chest X-ray, at the time of initiation of medication, and at the completion of 1st, 2nd, 4th, and last month. High resolution ultrasonography (HR-USG) thorax was done at the end of 6th month of treatment. Blood glucose levels, body temperature, weight, and blood pressure were recorded at each visit. The rate of reabsorption was calculated by drawing a line on chest X-ray from the lung apex to the mid-point of the curve of the fluid level on the diseased lung (X) and to the mid-point of the hemi-diaphragmatic curve of the contralateral hemithorax (Y). X was divided by Y and determined value was recorded as a percentage (Fig. 1). This index reflects the amount of fluid remaining in the pleural cavity and its evolution in time indicates the degree of reabsorption of the effusion. The amount of pleural effusion at initial presentation was graded as follows:

| Small       | ≤1/3rd of a hemithorax |
|-------------|------------------------|
| Moderate    | 1/3-2/3rd of a hemithorax |
| Large       | >2/3rd of a hemithorax  |

Side effects of corticosteroids and ATT were carefully recorded throughout the study period.

Results
Seventy-six patients were included in this study during one year duration. All these patients were eligible for final analysis, and were divided into two equal groups with 38 in the case group & control group each. The demographic characteristics of the 76 randomized subjects in form of age, sex, socioeconomic status and occupation were compared (Fig. 2). Age of study population ranged from 7-75 years, median age 31 years and mean age of patients was 35.46±15.89 years. Proportional differences in age of Cases and Controls was found but this difference was not found to be statistically significant (p=0.289). Out of 76 cases enrolled in the study, 55 (72.37%) were males and rest were females (n=21; 27.63%). Though proportion of females was higher in Controls (28.95%) as compared to Cases (26.32%) but difference in gender of cases and controls was not found to be statistically significant (p=0.798). Socio-economic class of majority of cases was Middle class (n=49; 64.47%), rest of the cases (n=27; 36.53%) belonged to Lower class. Proportion of middle class patients was higher in Controls (68.42%) as compared to Cases (60.53%), but difference in socio-economic class between Cases and Controls was not found to be statistically significant (p=0.472). Despite proportional differences in occupation of Cases and Controls, difference in occupation of these two groups was not found to be statistically significant (p=0.182).

At initiation of treatment amount of pleural fluid in 57(75%) patients was small while that was moderate in 19(25%) patients. Patients with moderate amount of pleural fluid at the start of treatment were more in case (34.21%) group as compared to control (15.79%) group, but difference in amount of pleural fluid at initiation of treatment in case & controls was not found to be statistically significant (p=0.064). Comparison was done between the biochemical/hematological variables in cases in the Controls and Cases groups. None of the biochemical/hematological showed statistically significant differences (Table 1).

Duration of resolution of fever and cough in control group was longer that than in cases and was found to be statistically significant. Although duration of resolution of chest pain in control group was longer than that in case group, but this difference was not found to be statistically significant.
significant. Duration of resolution of breathlessness in control group was found to be significantly longer on statistical analysis than that in the cases (Table 2). It was also observed that the rate of resolution of effusion was significantly higher in case group as compare to control group up to the end of 2nd month and was found to be insignificant in the later months (Table 3). Unexpectedly at the end of 6th month, 21 patients from the control group and 14 patients from the case group developed pleural thickening questioning the long lasting beneficial effect of steroid as adjuvant to ATT. The pleural thickness in overall patients ranged from 0.9-12 mm and mean pleural thickness in study population was 3.00±2.67 mm. Though pleural thickness at 6 months in cases (2.71±2.71 mm) was lower than that of controls (3.19±2.69 mm) but difference in pleural thickness of patients belonging to the case and control group was not found to be statistically significant (p=0.607) (Table 4).

Fig. 1: Parameters for calculation of rate of reabsorption of pleural fluid

Fig. 2: Comparison of demographic variables in case & control group
In our study, the mean duration of resolution of symptoms other than chest pain in case group was lesser than of the control group and the difference was found to be statistically significant (p<0.05). This indicates the beneficial role of addition of steroid to ATT. Unfortunately the mean duration of resolution of chest pain in case group was 6.53 days as compare to control group (8.36 days). The difference was not statistically significant (p<0.05). This is in accordance to the study done by Lee et al., [22]. Similar results were also noted by Paley et al., [23], Mathur et al., [24] and Tani et al., [25].

Thus in the present study we observed a rapid resolution of the effusion up to the end of 2nd month after introduction of prednisolone as an adjuvant to ATT in the case group. The rate of resolution measured after 1st and 2nd months of treatment is 86.24% and 91.32% in steroid treated group (case) compared with 82.68% and 88.18% in control group. There was also a significant rapid resolution of effusion in the 4th and 6th month in the case group comparing to the control group. This observation was in accordance to the study done by Galarza et al., [26]. As the prednisolone was given for one month of the start of treatment and the rapid resolution was seen in the same initial months as compared to the later months it clearly indicated its adjunctive beneficial role.

**Table 1:** Comparison of biochemical/hematological variables in cases and controls

|                      | Cases (n=38) | Controls (n=38) | Student 't' test |
|----------------------|-------------|-----------------|-----------------|
|                      | n | Mean | SD | n | Mean | SD | 't'  | 'p'  |
| TLC/(cumm.)          | 38 | 2082.66 | 1854.30 | 38 | 2730.26 | 2846.25 | -1.175 | 0.244 |
| DLC (N)              | 38 | 9.63 | 4.98 | 38 | 12.50 | 10.10 | -1.570 | 0.121 |
| DLC (L)              | 38 | 90.37 | 4.98 | 38 | 87.50 | 10.10 | 1.570 | 0.121 |
| Serum Protein (g/dl) | 38 | 7.30 | 0.79 | 38 | 7.05 | 0.80 | 1.385 | 0.170 |
| Pleural Fluid Protein (g/dl) | 38 | 5.31 | 0.64 | 38 | 5.63 | 0.76 | -1.971 | 0.052 |
| Pleural Fluid Glucose (mg/dl) | 38 | 81.34 | 30.38 | 38 | 82.05 | 24.21 | -0.113 | 0.911 |
| Pleural Fluid ADA (U/L) | 38 | 70.61 | 19.88 | 38 | 73.47 | 24.00 | -0.567 | 0.572 |

**Table 2:** Comparison of duration of resolution of symptoms (in days) in case and control group

|                      | Cases (n=38) | Controls (n=38) | Student 't' test |
|----------------------|-------------|-----------------|-----------------|
|                      | n | Mean | SD | n | Mean | SD | 't'  | 'p'  |
| Fever                | 37 | 6.35 | 2.90 | 38 | 8.58 | 3.22 | -3.147 | 0.002 |
| Cough                | 34 | 6.38 | 2.49 | 36 | 7.75 | 2.39 | -2.344 | 0.022 |
| Chest Pain           | 17 | 6.53 | 2.85 | 33 | 8.36 | 3.55 | -1.842 | 0.072 |
| Breathlessness       | 29 | 6.59 | 2.63 | 36 | 8.22 | 3.15 | -2.237 | 0.029 |

**Table 3:** Comparison of rate of resolution (in %) at different time intervals in cases and controls

|                      | Cases (n=38) | Controls (n=38) | Student 't' test |
|----------------------|-------------|-----------------|-----------------|
|                      | n | Mean | SD | n | Mean | SD | 't'  | 'p'  |
| 1 month              | 38 | 86.24 | 7.05 | 38 | 82.68 | 8.97 | 1.920 | 0.059 |
| 2 months             | 38 | 91.32 | 6.98 | 38 | 88.18 | 7.97 | 1.822 | 0.072 |
| 4 months             | 38 | 94.87 | 5.86 | 38 | 93.68 | 6.39 | 0.841 | 0.403 |
| 6 months             | 38 | 97.61 | 4.30 | 38 | 96.63 | 4.76 | 0.936 | 0.352 |

**Table 4:** Comparison of pleural thickening (in mm) at 6th month in cases & control

| Group       | N  | Min | Max | Median | Mean | SD |
|-------------|----|-----|-----|--------|------|----|
| Cases       | 14 | 0.9 | 9   | 1.5    | 2.71 | 2.71 |
| Controls    | 21 | 1   | 12  | 2      | 3.19 | 2.69 |
| **Total**   | 35 | 0.9 | 12  | 2      | 3.00 | 2.67 |

'\( t' = 0.519; p=0.607 \)

**Discussion**

The present was conducted in the department of Respiratory Medicine, King George Medical University, Lucknow, on seventy six diagnosed cases of tubercular effusion for one year. There was no significant difference in demography and disease burden among the patients included in the case and control groups. In our study, highest number of cases belonged to the age group of 21-30yr (38.15%), followed by 31-40 years (18.42%). This is in accordance to the study done by Parikh et al., [18] and Aktogu et al., [19]. In present study, male patients (72.36%) were more than female patients (27.64%) which is in accordance with the studies done by Aktogu et al., [19] and Harish et al., [20]. In our study, 49 (64.47%) patients belong to urban area and rest of the 27 (35.52%) patients belong to the rural area. This is in accordance to study done by Amer et al., [21].
A study done by Chhabra et al., [27] in India concluded that corticosteroids in pleural TB reduces the fibrotic sequel. In our study there was an early resolution of clinical symptoms and signs i.e. fever, chest pain, dyspnoea with no difference in development of residual pleural thickening or adhesions on follow-up. Residual functions were similar at completion on treatment.

In our study, out of 76 patients, 35 developed pleural thickening and most of them were from the control group which were not given steroid. The mean pleural thickening in the case group was 2.71 mm while 3.19 mm in the control group with standard deviation of 2.71 and 2.69 respectively reflecting the favourable response of steroid addition in the Case group. This was in accordance with the study done by Lee et al., [22] and Galarza et al., [26].

Side effect of anti-tubercular therapy was observed in 3 patients (ATT induced hepatitis in 1 case, Skin rashes in 1 case, 1 controls). None of the patient either case or control develop side effect related to steroid.

Conclusion
Thus we conclude from our study that the addition of corticosteroids antitubercular chemotherapy, will resolve the clinical symptoms more quickly and hasten the absorption of pleural effusion in patients with tuberculous pleuritis. When corticosteroids were added to the antitubercular chemotherapy, the absorption of the pleural fluid was hastened. Unfortunately there was no significant beneficial role of steroid on pleural thickening in the case group.

Thus corticosteroid may be judiciously used by adding it in the initial course of ATT to foreshorten the acute phase of this morbid disease and to prevent damage of pleura with lowering the rate of fibrosis and thickening and better control of symptoms. However current National guidelines do not remark on the adjunctive use of steroid along with ATT still one can pre-judiciously prescribe it keeping in mind all the pros and cons.

Limitations
The present study was conducted on the basis of available resources only and thus the diagnosis of all the cases could not be confirmed by the demonstration of the causative microorganism. The treatment was provided on the basis of ADA level and the lymphocyte predominance in the pleural fluid.

Conflict of interest
Nil.

Acknowledgement
None.

References
1. Mohan A, Sharma S K. Epidemiology. In: Sharma S K, Mohan A, editors. Tuberculosis. New Delhi: Jaypee Brothers Medical Publishers; 2001 p.14-29.
2. Fanning A. Tuberculosis: 6. Extrapulmonary disease. CMAJ. 1999;160:1597-603.
3. Lee MP, Chan JW, Ng KK, Li PC. Clinical manifestations of tuberculosis in HIV-infected patients. Respiroil. 2000;5:423-6.
4. Poprawski D, Pitsissutitum P, Tansuphasawadul S. Clinical presentations and outcomes of TB among HIV-positive patients. Southeast Asian J Trop Med Public Health. 2000;31(Suppl 1):140-2.
5. Seibert AF, Haynes J Jr, Middleton R, et al. Tuberculous pleural effusion. Twenty-year experience. Chest. 1991;99:883-6.
6. Bollinger CT, de Kock MA. Influence of a fibrothorax on the flow-volume curve. Respir. 1988;54:197-200.
7. Candela A, Andujar J, Hernandez L. Functional sequel of tuberculous pleurisy in patients correctly treated. Chest 2003;123;1996-2000.
8. Light RW. Update on tuberculous pleural effusion. Respirol. 2010;15:451-8.
9. Diaco AH, Van de Wal BW, Wyser C. Diagnostic tools in tuberculous pleurisy: a direct comparative study. Eur Respir J. 2003;22:589-91.
10. Light RW. Update on tuberculous pleural effusion. Respirol. 2010;15:451-8.
11. Koegelenberg CF, Bolliger CT, Theron J. Direct comparison of the diagnostic yield of ultrasound assisted Abrams and Tru-Cut needle biopsies for pleural tuberculosis. Thorax. 2010;65:857-62.
12. Lee YC, Rogers JT, Rodriguez RM. Adenosine deaminase levels in nontuberculous lymphocytic pleural effusions. Chest. 2001;120:356-61.
13. Jiménez Castro D, Díaz Nuevo G, Pérez-Rodríguez E. Diagnostic value of adenosine deaminase in nontuberculous lymphocytic pleural effusions. Eur Respir J. 2003;21:220-4.
14. Mathur KS, Prasad R, Mathur JS. Intrapleural hydrocortisone in tuberculous pleural effusion. Tubercle. 1960;40:358–60.
15. Menon NK. Steroid therapy in tuberculous effusion. Tubercle. 1964;45:17-20.
16. Smith MHD, Matsaniotis N. Treatment of tuberculous pleural effusion with particular reference to adrenal corticosteroids. Pediatrics. 1958.
17. Miller KD, Barnette R, Light RW. Stability of adenosine deaminase during transportation. Chest. 2004;126:1933-9.
18. Parikh P, Odhwani J, Ganagajalia C. Study of 100 cases of tubercular therapy was observed in 3 cases. Menon NK. Steroid therapy in tuberculous effusion. Tubercle. 1964;45:17-20.
19. Aktooglu S, Yorgancioglu A, Cirak K, Kose T, Dereli SM. Clinical spectrum of pulmonary and pleural tuberculosis: A report of 5480 cases. Eur Respir J. 1996;9:2031-5.
20. Harish G, Vivek. Clinical profile of pleural effusion patient: A tertiary care hospital study. J Evid Based Med Health Care ICV. 2015;78-84.
21. Khan AH, Ahar S, Sulaikman S. Pleural Tuberculosis and its Treatment Outcome. Trop J Pharm Res. 2013;12(4):623-627.
22. Lee, CH, Wang, WJ. Corticosteroids in the treatment of tuberculous pleurisy: a double-blind, placebo-controlled, randomized study. Chest. 1988;94:1256-9.
23. Paley SS, Mihaly SI, Mais EL, Gittens SA, Lupini B. Prednisone in the treatment of tuberculous pleural effusions. Am Rev Tuberc. 1959;79:307-14.
24. Mathur KS, Prasad R, Mathur JS. Intrapleural hydrocortisone in tuberculous pleural effusion. Tubercle. 1960;41:358-62.
25. Tani P, Poppius H, Makipaja J. Cortisone therapy for exudative tuberculous pleurisy in the light of a follow-up study. Acta Tuberc Scand. 1964;44:303-9.
26. Galarza, I, Canete, C, Granados, A. Randomised trial of corticosteroids in the treatment of tuberculous pleurisy. Thorax. 1995;50:1305-307.
27. Chhabra N, Dixit R. Adjunctive corticosteroid therapy in tuberculous management. IJPSR. 2011;2(1):10-5.

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