DOI: 10.7860/JCDR/2022/57821.16726

Original Article

Internal Medicine Section

Role of Corticosteroids in Tubercular Pleural Effusion: A Prospective Interventional Study from a Tertiary Care Teaching Hospital, Telangana, India

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ABSTRACT

Introduction: Tuberculosis is a major public health problem in majority of the developing countries. Pleural effusion develops when fluid accumulates between the parietal and visceral pleura.

Aim: To evaluate the efficiency of corticosteroids in rapid clinical and radiological resolution of Tubercular Pleural Effusion (TPE). Also to study the recurrence of pleural effusion and find incidence of pleural fibrosis in patients treated with corticosteroids.

Materials and Methods: This prospective interventional study was conducted at Government Chest Diseases and TB hospital (tertiary care teaching hospital), Telangana, India, from October 2014 to October 2016. Total 80 patients with TPE were divided into two groups. Steroid group (n=40), patients received standard Antitubercular Treatment (ATT) that was alternate day regimen along with prednisolone 0.75 mg/kg body weight per day for two weeks there after tapering of the dose done every second weekly in next four weeks. Non steroid group (n=40), patients received standard ATT alone that was alternate day regimen under Directly Observed Treatment Short course (DOTS) therapy based on Revised National TB Control Programme (RNTCP) guidelines respectively. All patients were followed in the Outpatient Department at the end of second, fourth, sixth, 24th week. At every follow-up visit, history obtained from patients regarding symptoms and chest radiographs for comparison of reabsorption of pleural fluid between two groups. At the end of treatment ultrasound of the chest was performed to confirm the presence of pleural thickening seen on chest radiograph. Descriptive measures obtained included as mean and standard deviation. The association between two categorical variables done by using Chi-square test. The p-values <0.05 was considered as statistically significant.

Results: There was early initiation of symptomatic relief in patients treated with steroid group as compared to non steroid group (p-value <0.001). Average duration for symptomatic relief in steroid group was 3.42 days (range 1-7 days) and in non steroid group 8.3 days (range 1-42 days). There was significant difference between two groups in duration taken for symptomatic relief (p-value <0.001).

Conclusion: Results of the present study suggest that corticosteroids still play some role in the treatment of TPE. Addition of the corticosteroids to the standard ATT exerts more rapid relief of clinical symptoms. The rapidity in pleural fluid absorption is not influenced significantly by adding corticosteroids to the ATT. There was no recurrence of pleural effusion after addition of corticosteroids to ATT. The incidence of pleural thickening was not influenced by steroids.

Keywords: Extrapulmonary, Pleural fibrosis, Pleural thickening, Prednisolone, Tuberculous pleuritis

INTRODUCTION

Tuberculosis (TB) is a major public health problem in majority of developing countries [1]. In most of the cases TB is caused by a pathogenic bacteria *Mycobacterium tuberculosis*. It belongs to the family of *Mycobacteriaceae* [2]. An estimated nine million people developed active TB in the year 2013 with 1.5 million deaths attributed to the disease [3]. Total 80% of the TB affects the lungs and remaining 20% Extrapulmonary TB (EPTB) primarily involves the lymph nodes and pleura. Pleural disease is one of the most common extrapulmonary involvement in TB in developing countries [4]. The lung parenchyma, the mediastinum, the diaphragm, and the rib cage are covered by the serous membrane called the pleura [5]. In normal individuals the mean amount of fluid in the right pleural space is 8.4±4.3 mL. Normally, the volume of fluid in the right and left pleural spaces is quite similar [6].

Pleural effusion develops when fluid accumulates in between the visceral and parietal pleura [7]. One-fifth of new TB cases notified in 2014 in India were extrapulmonary [8]. Tubercular Pleural Effusion (TPE) is the second common form, constituting about 28% of EPTB [9-11]. In many different diseases pleural effusions can occur as a complication. The first step in assessing a pleural effusion is to determine whether it is a transudate or exudate. Initially this was carried out by taking history and performing physical examination. The biochemical analysis of pleural fluid is considered later [12].

Light's criteria was used to categorise the pleural effusions into transudative or exudative [13]. Even after extensive effort as many as 15-20% of all pleural effusions remain undiagnosed [14]. In all patients with an undiagnosed pleural effusion it is essential to consider the possibility of tuberculous pleuritis [15]. Pleural biopsy provides diagnostic value for patients with exudative effusions who remain undiagnosed after thoracentesis [16].

Even without specific Antitubercular Treatment (ATT), some of the TPEs resolve spontaneously. However, two-third of patients with TPE may show clinical symptoms with pleural thickening later. It is evaluated that corticosteroids like prednisolone enhance the resolution of pleural effusion as well as reduce the clinical symptoms [17].

It was found that corticosteroids like prednisolone extensively decreased the duration of symptoms by about 4.3 days in some trails [18,19]. Unexpectedly, Engel ME et al., found that corticosteroids significantly reduced the risk of pleural thickening by about 31% [17]. The role of corticosteroids in the management of TPE is controversial. Hence, the present study was undertaken to evaluate:

i) The efficiency of corticosteroids in rapid clinical and radiological resolution of TPE.

ii) The recurrence of pleural effusion in patients on corticosteroids.

iii) The incidence of pleural fibrosis in patients treated with corticosteroids.

MATERIALS AND METHODS

This prospective interventional study was conducted at Government Chest Diseases and TB hospital (tertiary care teaching hospital), Telangana, India, from October 2014 to October 2016, on 80 patients with TPE. This study was approved by the Institutional Ethics Committee (MGM/KMC) Warangal (KMC/IEC/O79). An informed written consent was taken from all the patients involved in the study after explaining regarding the study.

Inclusion criteria: Patients aged between 20-50 years and presenting with mild and moderate TPE, who were not treated with corticosteroids previously were included in the study. For patients included in the study, baseline chest radiograph was taken and size of pleural effusion was estimated according to the area of opacification caused by the pleural fluid on the chest radiograph [20]. Patients was also assessed for symptomatic relief like decrease in chest pain, dyspnea, dry cough.

Exclusion criteria:

- Age <20 and >50 years
- Patients with massive pleural effusion, malignant pleural effusion and pleural effusion due to other conditions other than tuberculosis, loculated pleural effusion, bilateral pleural effusion, empyema, parapneumonic effusions, pericardial effusion and ascities.
- Patients with parenchymal diseases including tuberculosis and Human Immunodeficiency Virus (HIV) patients
- Defaulters or relapse cases of TPE
- Critically ill patients
- Patients with co-morbid conditions like diabetes, hypertension, Chronic Kidney Disease (CKD) and patients with cushing syndrome.

Total 80 patients with TPE were divided into two groups,

- Steroid group (n=40): Patients received standard ATT that was alternate day regimen along with prednisolone 0.75 mg/kg body weight per day for two weeks there after tapering of the dose done every second weekly in next four weeks.
- Non steroid group (n=40): Patients received standard ATT alone that was alternate day regimen under Directly Observed Treatment Short-course (DOTS) therapy based on Revised National TB Control Programme (RNTCP) guidelines respectively [21].

Study Procedure

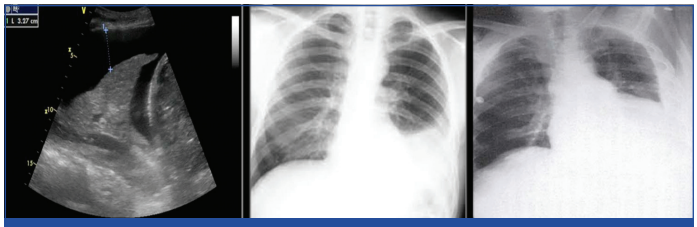
All patients were followed in the Outpatient Department at the end of 2nd, 4th, 6th, 24th week (at the end of treatment). At every follow-up visit, history obtained from patients regarding symptomatic relief and chest radiographs for comparison of reabsorption of pleural fluid between two groups.

Reduction of pleural effusion:

- 50% reduction in pleural effusion: If the amount of fluid decreased to a lower grade. It can be stated as clear.
- 25% reduction in pleural effusion: If there was reduction in the amount of fluid but still within the same grade. It can be stated as unclear.

The obliteration of costophrenic angle was used when the angle was >90° [20].

Pleural thickening: The pleural thickening was measured in millimeters (mm), a visible line between the inside of the chest wall and the outer border of the lung in response to inflammation of the pleura in TPE. The thickness of the line may be 1-10 mm. The pleural thickening results from fibrosis of the visceral pleural surface [20]. At the end of treatment ultrasound of the chest was performed to confirm the presence of pleural thickening seen on chest radiograph [Table/Fig-1-3] [22].



[Table/Fig-1]: Ultrasound showing pleural effusion.
[Table/Fig-2]: Chest X-ray Posteroanterior (PA) view showing pleural effusion.
[Table/Fig-3]: Chest X-ray lateral decubitus view showing pleural effusion. (Images from left to right)

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 16.0. Numerical data was entered as such. Categorical data was appropriately coded. Descriptive measures obtained included as mean and standard deviation. The association between two categorical variables done by using Chi-square test. Summary of the data was done by number and percentage. The p-values <0.05 was considered as statistically significant.

RESULTS

Both groups were identical in terms of sex, age, duration of symptoms and initial amount of pleural effusion.

Initiation of symptomatic relief in TPE: The symptomatic relief in steroid group was started within three days. In non steroid group, symptomatic relief started within seven days. There was earlier initiation of symptomatic relief among patients of steroid group as compared with non steroid group. The difference was statistically significant (p-value <0.05) [Table/Fig-4].

Group	Initiation of symptomatic relief (days) Median (IQR)	p-value (Mann-Whitney U test)
Steroid (n=40)	3 (3-4)	<0.001
Non steroid (n=40)	7 (7-10)	

[Table/Fig-4]: Initiation of symptomatic relief among study groups with TPE.
p-values <0.05 was considered as statistically significant; IQR: Inter quartile range

All 40 patients in steroid group showed symptomatic relief with an average duration of 3.42 days (range 1-7) and in non steroid group showed symptomatic relief with an average duration of 8.3 days (range 1-42). The difference was statistically significant (p-value <0.001) [Table/Fig-5].

Duration (on day)	Steroid group	Non steroid group	p-value (Chi-square test)
	Number of patients on each day		
1	2	-	<0.001
2	5	-	
3	18	1	
4	8	1	
5	4	4	
6	2	1	
7	1	17	
10	-	10	
12	-	2	
14	-	4	

[Table/Fig-5]: Time duration taken for symptomatic relief among study groups with TPE.
p-values <0.05 was considered as statistically significant

Out of 40 patients in steroid group, 23 patients showed complete radiological resolution [Table/Fig-6]. In the non steroid group, out of 40 patients, 22 patients showed complete radiological resolution. There was no difference between two groups in radiological resolution at the end of treatment. The result was statistically not significant (p-value=0821).

Radiological resolution of TPE	Steroid group n (%)	Non steroid group n (%)	p-value (Chi-square test)
Clear (Grade 0-1)	23 (57.5)	22 (55)	0.821
Unclear (Grade 2-3)	17 (42.5)	18 (45)	
Total	40 (100)	40 (100)	

[Table/Fig-6]: Radiological resolution among study groups with TPE.
p-values <0.05 was considered as statistically significant

Total 23 patients in steroid group showed radiological resolution. Out of 23 patients, 11 patients were showed radiological resolution in less than four weeks. Total eight patients showed radiological resolution between 4-6 weeks and four patients took more than six weeks [Table/Fig-7].

Duration (week)	Steroid group n (%)	Non steroid group n (%)	p-value
<4 weeks	11 (47.8)	4 (18.2)	0.108
4-6 weeks	8 (34.8)	12 (54.5)	
>6 weeks	4 (17.4)	6 (27.3)	
Total	23 (100)	22 (100)	

[Table/Fig-7]: Duration taken for clear radiological resolution patients among study groups with TPE.
p-values <0.05 was considered as statistically significant

In non steroid group, 22 patients showed radiological resolution. Out of 22 patients, only four patients showed radiological resolution within four weeks, 12 patients showed between 4-6 weeks, six patients taken more than six weeks.

There was rapid reabsorption of pleural fluid in patients in steroids group as compared with non steroid group, but the result was not significant statistically (p-value >0.05).

Incidence of pleural fibrosis/pleural thickening in TPE: Out of 40 patients in steroid group, 17 patients improved with no radiological clearance at the end of treatment, five patients showed blunting of costophrenic angles and 12 patients had pleural thickening at the end of treatment [Table/Fig-8].

Outcome	Steroid group n (%)	Non steroid group n (%)	p-value
Clear resolution	23 (57.5)	22 (55)	0.391
Blunting of costophrenic angle	5 (12.5)	2 (5)	
Pleural thickening	12 (30)	16 (40)	
Total	40 (100)	40 (100)	

[Table/Fig-8]: Incidence of treatment outcomes among study groups with TPE.
p-values <0.05 was considered as statistically significant

Out of 40 patients in non steroid group, two patients had blunting of Costophrenic (CP) angle and 16 patients had pleural thickening. There was no statistical significance in the incidence of pleural fibrosis/pleural thickening between two groups (p-value >0.05).

Recurrence of pleural effusion in steroid group: No patient experienced a recurrence of pleural effusion in either treatment group.

Side-effects: Serious side-effects with corticosteroids were not observed during this study. Only two patients developed transient impaired glucose tolerance after administration of prednisolone and this side-effect subsided after tapering of the dose of prednisolone. None of the patients developed the symptoms of cushing's syndrome like moon face, buffalo hump, abdominal stretch marks, thinning of legs.

DISCUSSION

The role of corticosteroids in the treatment of TPE is controversial. The administration of corticosteroids did not decrease the degree of residual pleural thickening [15].

Symptomatic improvement: In the present study, out of 80 patients, 40 patients treated with prednisolone showed early initiation of symptomatic improvement within three days as median compared to non steroid group, which showed initiation of symptomatic improvement within seven days. With ATT, most patients become afebrile within two weeks, and pleural fluid resorbed within six weeks [20]. In the present study, corticosteroids hastened the recovery of constitutional symptoms and led to early initiation in symptomatic relief. In a previous study conducted by Lee CH et al., patients receiving corticosteroids were free from complaints within two days after treatment, clinical symptoms and signs subsided an average of 2.4 days (range 1-7) in the steroid group and 9.2 days (range 1-75) in non steroid group and showed the positive effect of the additional use of corticosteroids in TPE, in terms of a more rapid relief of symptoms [18].

Radiological resolution: In a previous study conducted by Galarza I et al., reported that 93% of patients showed radiological resolution at the end of one month in steroid group and 89% of patients showed radiological resolution in non steroid group [23]. There was no significant difference between two groups. In the present study, 47.82% of patients showed radiological resolution at the end of one month of treatment in steroid group as compared with non steroid group (18.18%). The present study shows significant difference between two groups in radiological resolution at the end of one month of treatment. The present study is different from previous study due to less sample size and short period of follow-up [20].

Duration taken for radiological resolution in TPE: In the present study, out of 40 patients in steroid group, 23 patients showed radiological resolution within an average duration of 23.3 days (3.3 weeks) and 40 patients in non steroid group showed radiological resolution within an average duration of 29.26 days (4.18 weeks). There was no big difference in duration taken for radiological resolution between two groups, but early disappearance of fluid occurred in steroid group as compared with non steroid group. Complete resolution of pleural fluid after initiation of treatment can take 6-12 weeks [24].

A previous study conducted by Lee CH et al., roentgenologic evidence of clearing of the lung field, with visualisation of the diaphragm and costophrenic angle occurred at an average of 54.5 days in steroid group in contrast to an average of 123.2 days in non steroid group [18]. Another study conducted by Bang JS et al., an average duration for radiological resolution in steroid group was 88 days as compared to 101 days in non steroid group [19]. The present study deviated from other studies because of difference in duration of observation. In this study, follow-up done at the end of second week, fourth week, 6th week and 24th week. When compared to present study there is a huge difference observed in the above cited study duration. This is because in present times the ATT protocols have changed and management regimens have become more aggressive.

Incidence of pleural fibrosis/pleural thickening in TPE: In the present study, out of 40 patients in steroid group 17 patients improved with pleural fibrosis/pleural thickening and 18 patients in non steroid group improved with pleural fibrosis/pleural thickening. About half of the patients with TPE developed Residual Pleural Thickness (RPT) despite appropriate treatment. A more than 2 mm pleural thickness (at the point of maximal thickness) at 24 weeks was defined as residual pleural thickening [25]. Pleural effusion causes blunting of the costophrenic angle. RPT is a consequence of an inflammatory mechanism in TPE [25]. Chest X-ray is more readily available and inexpensive and also reported that High-resolution Computed

Tomography (HRCT) was not more sensitive than conventional chest radiography in diagnosing pleural thickening [26]. The RPT exceeding 10 mm in size may have important clinical and functional consequences [27]. Repeated thoracentesis does not appear to alter the degree of residual pleural thickening [27].

In a previous study conducted by Wyser C et al., reported that 17 patients in steroid group and 18 patients in non steroid group showed pleural thickening at the end of treatment, which is similar to the present study [25]. Another study conducted by Bang JS et al., reported that 17 patients in steroid group and 32 patients in non steroid group showed pleural thickening at the end of treatment, which is close to the present study [19].

Limitation(s)

The sample size was small and short period of follow-up was done. The present study was to mild and moderate pleural effusions and more studies need to be done on patients with large or massive pleural effusions to know the efficiency of corticosteroids in pleural fluid reabsorption and effect on pleural thickening.

CONCLUSION(S)

Results showed that corticosteroids still play some role in the treatment of TPE. Addition of the corticosteroids to the standard ATT provides rapid relief of clinical symptoms. The rapidity in pleural fluid absorption is not influenced significantly by adding corticosteroids to the ATT. There was no recurrence of pleural effusion after addition of corticosteroids to ATT and non steroid group. The incidence of pleural thickening was not influenced by steroids. Further large studies are needed to be re-emphasise the beneficial role of corticosteroids in the treatment of TPE.

REFERENCES

[1] Porcel JM. Tuberculous pleural effusion. Lung. 2009;187(5):263-70.
[2] Smith I. Mycobacterium tuberculosis pathogenesis and molecular determinants of virulence. Clin Microbiol Rev. 2003;16(3):463-96.
[3] World Health Organization. Global Tuberculosis Report 2014. Geneva: World Health Organization, 2014. Available online: https://apps.who.int/iris/bitstream/handle/10665/137094/9789241564809_eng.pdf?sequence=1. Accessed 10 December 2014.
[4] Sharma SK, Mohan A. Tuberculosis. 2nd. New Delhi: Jaypee Brothers Medical Publishers; 2009;245.
[5] Light RW. Pleural effusions. Med Clin North Am. 2011;95(6):1055-70.
[6] Noppen M, Waele MD, Li R, Gucht KV, Haese JD, Gerlo E, et al. Volume and cellular content of normal pleural fluid in humans examined by pleural lavage. Am J Respir Crit Care Med. 2000;162(3 Pt 1):1023-26.
[7] Saguil A, Wyrick K, Hallgren J. Diagnostic approach to pleural effusion. Am Fam Physician. 2014;90(2):99-104.
[8] Chennaiyan B, Bhatt AN, Kancherla R, Kuriakose CK, Dev AV, Philip GA. Validity of tuberculous pleuritis diagnosed in a resource-constrained setting in Dindigul district of Tamil Nadu. J Family Med Prim Care. 2016;5(3):615-18.
[9] Prakasha SR, Suresh G, D'sa IP, Shetty SS, Kumar SG. Mapping the pattern and trends of extrapulmonary tuberculosis. J Glob Infect Dis. 2013;5(2):54-59.
[10] Arora VK, Gupta R. Trends of extra-pulmonary tuberculosis under revised national tuberculosis control programme: A study from South Delhi. Indian J Tuberc. 2006;53:77-83.
[11] Maldhure BR, Bedarkar SP, Kulkarni HR, Paplnwar SP. Pleural biopsy and adenosine deaminase in the pleural fluid in the diagnosis of tubercular pleural effusion. Indian J Tuberc. 1994;41:161-64.
[12] Maskell NA, Butland RJA; Pleural Diseases Group, Standards of Care Committee, British Thoracic Society. BTS guidelines for the investigation of a unilateral pleural effusion in adults. Thorax. 2003;58(Suppl 2):ii8-ii17.
[13] Udupa KA, Kumar VS, Manju R, Nandeesha H. Diagnostic accuracy of pleural fluid adenosine deaminase in tubercular pleural effusion. Int J Med Res Rev. 2016;4(8):1292-97.
[14] Saha K, Maji A, Bandyopadhyay A, Jash D. Diagnostic yield of closed pleural biopsy in undiagnosed exudative pleural effusions. Maedica (Bucur). 2021;16(1):34-40.
[15] Light RW. Update on tuberculous pleural effusion. Respirology. 2010;15(3):451-58.
[16] Koegelenberg CF, Diacon AH. Pleural controversy: Close needle pleural biopsy or thoracoscopy-which first? Respirology. 2011;16(5):738-46.
[17] Engel ME, Matchaba PT, Volmink J. Corticosteroids for tuberculous pleurisy. Cochrane Database Syst Rev. 2007;(4):CD001876. Doi: 10.1002/14651858.CD001876.pub2.
[18] Lee CH, Wang WJ, Lan RS, Tsai YH, Chiang YC. Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomized study. Chest. 1988;94(6):1256-59.
[19] Bang JS, Kim MS, Kwak SM, Cho CH. Evaluation of steroid therapy in tuberculous pleurisy: A prospective, randomized study. Tuberc Respir Dis. 1997;44(1):52-58.
[20] Mahmud T. Adjunct prednisolone versus anti tuberculous drugs alone for treatment of tuberculous pleurisy. Proceeding S.Z.P.G M.I. 2010;24(1):51-54.
[21] Central Tuberculosis Division Tuberculosis India: Annual Report of the Revised National Tuberculosis Control Programme. Directorate General of Health Services, Ministry of Health and Family Welfare. Government of India. Publications through Central TB Division-accessible from location: Government of India. 2011. Available from: http://www.tbcindia.nic.in/.
[22] Light RW. Radiographic Examinations Pleural Diseases. 2007, 5th. Baltimore: Lippincott Williams and Wilkins; pp. 211-14.
[23] Galarza I, Cañete C, Granados A, Estopà R, Manresa F. Randomised trial of corticosteroids in the treatment of tuberculous pleurisy. Thorax. 1995;50(12):1305-07.
[24] Han DH, Song JW, Chung HS, Lee JH. Resolution of residual pleural disease according to time course in tuberculous pleurisy during and after the termination of antituberculosis medication. Chest. 2005;128(5):3240-45.
[25] Wyser C, Walzl G, Smedema JP, Swart F, Schalkwyk EMV, Wal BWVD. Corticosteroids in the treatment of tuberculous pleurisy. A double-blind, placebo-controlled, randomized study. Chest. 1996;110(2):333-38.
[26] Kunter E, Ilvan A, Kilic E, Cerrahoglu K, Isitmangil T, Capraz F, et al. The effect of pleural fluid content on the development of pleural thickness. Int J Tuberc Lung Dis. 2002;6(6):516-22.
[27] Ferrer J. Pleural tuberculosis. Eur Respir J. 1997;10(4):942-47.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 22, 2022
- Manual Googling: Jun 17, 2022
- iThenticate Software: Jul 26, 2022 (16%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 16, 2022**
Date of Peer Review: **Jun 15, 2022**
Date of Acceptance: **Jul 25, 2022**
Date of Publishing: **Aug 01, 2022**