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Comparative Study to Assess the Efficacy of Intrapleural Corticosteroids versus Systemic Corticosteroids in the Treatment of Tubercular Pleural Effusion

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Abstract: **Background:** Tubercular Pleural Effusion is the second most common extrapulmonary site of involvement after lymph node tuberculosis. It is basically due to the type IV hypersensitivity reaction leading to the inflammation of the pleura. The healing of effusion arises with a legacy of pleural fibrosis resulting in clinically relevant pleural thickening and impairment of lung function. Corticosteroids have been shown to play an important role in treating and preventing pleural fibrosis when used along with ATT therapy in cases of Tubercular Pleural Effusion. Commonly corticosteroids are prescribed as oral/systemic therapy. Some studies have also shown that a single dose of intrapleural application of corticosteroids reduces complications like pleural fibrosis. Thus, this study was conducted to compare the efficacy of intrapleural corticosteroids versus systemic corticosteroids in the treatment of tubercular pleural effusion. **Methods**: A total of 100 patients with tubercular pleural effusion who presented to the Department of Pulmonary Medicine, GGSMCH Faridkot were included in the study for one year. Using a computer-generated random number table cases were randomised into two groups, Group I and Group II. Both groups were given Anti Tubercular Treatment (ATT) Fixed Dose Combination (FDC), according to the weight band as per National Tuberculosis Elimination Program (NTEP) guidelines. In addition to ATT, Group I was given Tablet Deflazacort P.O. 0.75mg/kg/day for 6 days thereafter tapering the drug 0.6mg/kg/day for 6 days → 0.45mg/kg/days for 6 days → 0.3mg/kg/day for 6 days → 0.15mg/kg/day for 6 days → stopped. In Group II, at the time of therapeutic aspiration, Intrapleural application of Dexamethasone 8mg, single time, was done. After this, patients of both groups were followed up at 4 weeks, 8 weeks, 12 weeks, and 24 weeks with chest x-rays and USG chest to estimate the level of pleural fluid (resolution/increase in pleural effusion) and pleural thickening (fibrosis/adhesions). **Results**: At the end of the study period, it was seen that a maximum of the patients (group I -- 64% and group II – 66%) showed resolution of pleural effusion during the first 8 weeks of treatment (not significant), whereas in 14% of the patients in group I and 4% in group II, pleural effusion did not resolve till the end of the study period (not significant). Residual Pleural Thickening was seen in 28% of patients in group I and 32% in group II (not significant). But more side effects of drugs were seen with oral corticosteroids (78%) than with intrapleural corticosteroids (40%) with a significant p-value. **Conclusion**: Keeping in view the fewer side effects of local corticosteroids, we emphasize that Intrapleural corticosteroids should be considered over Oral corticosteroids along with Anti- Tubercular Therapy in the treatment of Tubercular Pleural Effusion.

IndexTerms **- Tubercular pleural effusion, oral corticosteroids, intrapleural corticosteroids, residual pleural thickening.**

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by bacillus Mycobacterium tuberculosis (M. tb.). It has been one of the topmost killers of mankind through the ages, which mainly affects the lungs but it can involve other parts of the body also [1]. In the majority of patients, the lungs are involved in TB, but 25% of adults with TB initially present with the extra-pulmonary form, pleural TB being the second most common site of involvement after lymph node TB [2]. Pleural effusion is mainly determined because of an imbalance between hydrostatic and oncotic pressure present between the systemic and pulmonary circulation and pleural cavity [3]. Tuberculous pleurisy is basically due to inflammation of the pleura which occurs due to M. tb. It is thought to be a result of the rupture of a subpleural caseous focus (frequently recognized during an open pleural biopsy) in the lung into the pleural cavity. Inflammation is due to the hypersensitivity reaction to the bacillus which actually determines the occurrence and amount of effusion [4]. TPE, if treated, may resolve and heal without any long-term sequelae but without treatment, the resolution is slow, up to 65% will progress to active TB within 5 years [5,6]. However, in some instances, the 'healing' of effusions arises with a legacy of pleural fibrosis, possibly due to disordered fibrin turnover, whereby an imbalance between fibrin deposition and fibrinolysis occurs. Pleural fibrosis can result in clinically relevant pleural thickening and impairment of lung function. Estimates for this outcome vary, although some authors have cited pleural thickening in as many as 50% of cases. Therefore, the intent of treatment is to foreshorten the acute phase of the disease and to restore the integrity of the pleura preventing lasting fibrosis and thickening. TPE leads to residual pleural thickening (RPT) in a significant proportion of cases [7]. Studies have shown that corticosteroids play an important role in treating and preventing pleural fibrosis when used along with ATT therapy in cases of TPE [8]. Commonly corticosteroids are prescribed as oral/systemic therapy. Some studies have also shown that a single dose of intrapleural application of corticosteroids reduces complications like pleural fibrosis [9]. It has been seen that using corticosteroids may help in reducing the time to resolution of the symptoms and the pleural effusion (radiologically) in patients with

TPE. Along with this, corticosteroids may also reduce the risk of pleural fibrosis on chest X-rays (pleural thickening and pleural adhesions) after the disease has resolved. The use of oral/systemic corticosteroids can aggravate G.I.T. side effects (Nausea/ Vomiting, gastric ulcers) therefore using local corticosteroids is a better choice among such TPE [10]. Thus, keeping in view, the beneficial and systemic side effects of corticosteroids, the study was carried out to compare the efficacy of oral corticosteroids against single intrapleural corticosteroids in the treatment of TPE along with ATT, observing the disappearance of symptoms, disappearance of pleural effusion and RPT (radiologically) at multiple follow-ups at 4 weeks, 8 weeks, 12 weeks and 24 weeks of starting of the treatment.

RESEARCH METHODOLOGY

This study was carried out on 100 patients with Tubercular Pleural Effusion who presented to the Department of Pulmonary Medicine, Guru Gobind Singh Medical College, and Hospital, Faridkot during a study period of one year. Depending upon the chest x-ray, patients were divided into Mild/Moderate. The amount of pleural fluid not exceeding the 4th rib anteriorly (<1/3rd of hemithorax) -- mild pleural effusion, and pleural fluid located at the 2nd -4th rib ($1/3^{rd}$ – 2/3rd of hemithorax) -- moderate pleural effusion.

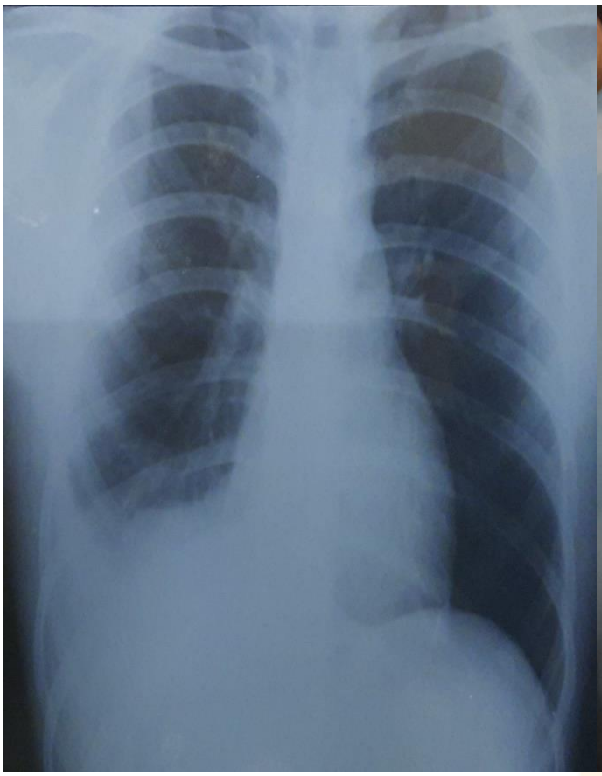


FIG. 1: Mild Pleural Effusion

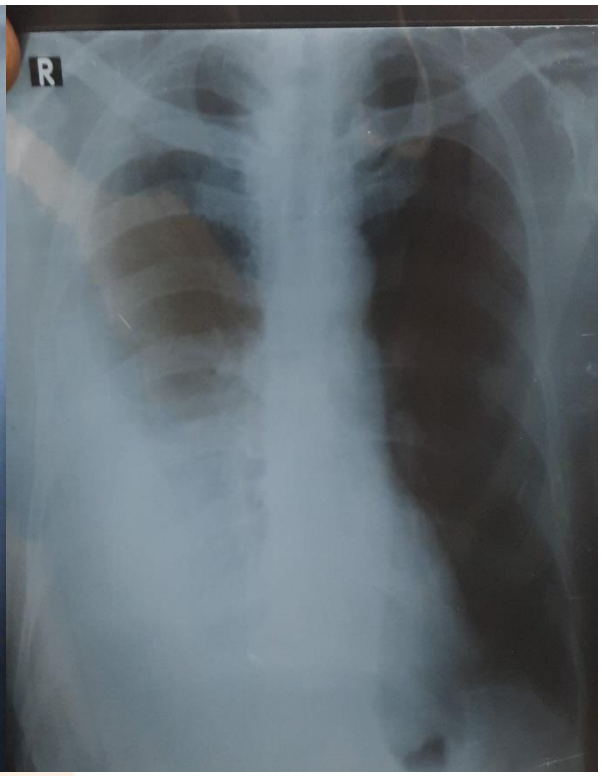
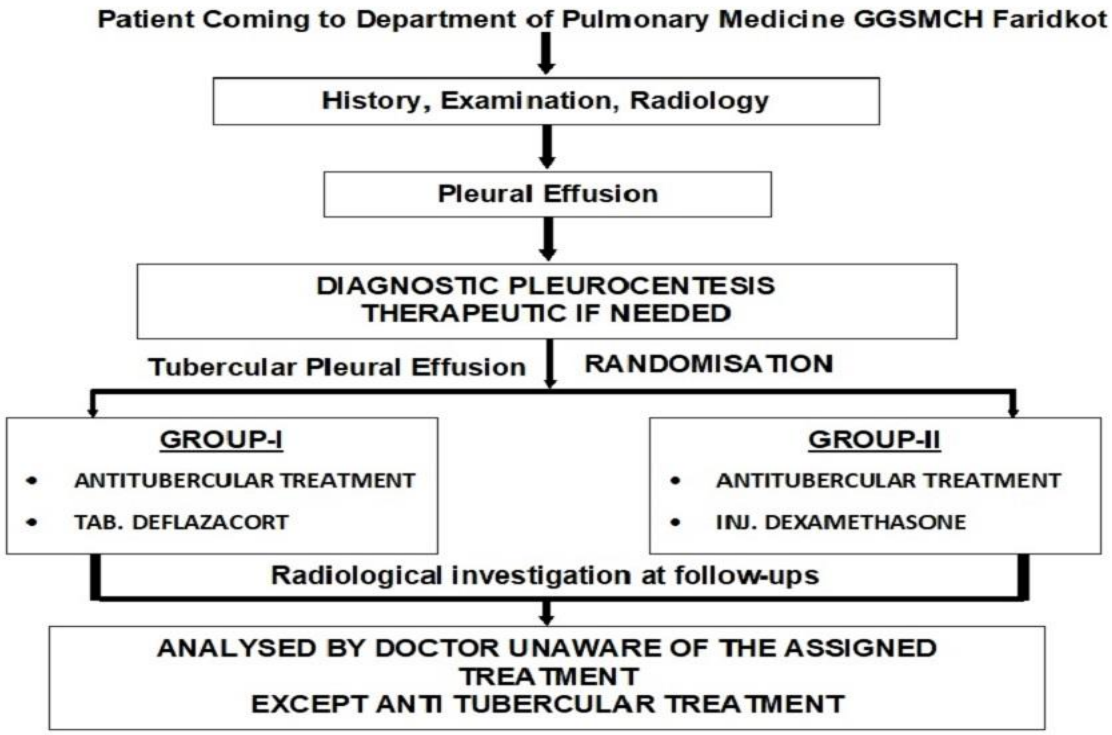


FIG. 2: Moderate Pleural Effusion

Therapeutic aspiration was done in all the patients. Using a computer-generated random number table cases were randomised into two groups, Group I and Group II. Both groups were given Anti Tubercular Treatment (ATT) Fixed Dose Combination (FDC), according to the weight band as per National Tuberculosis Elimination Program (NTEP) guidelines. In addition to ATT, Group I was given Tablet Deflazacort P.O. 0.75mg/kg/day for 6 days thereafter tapering the drug 0.6mg/kg/day for 6 days → 0.45mg/kg/days for 6 days → 0.3mg/kg/day for 6 days → 0.15mg/kg/day for 6 days → stopped. In Group II, at the time of therapeutic aspiration, Intrapleural application of Dexamethasone 8mg, single time, was done. After this, patients of both groups were followed up at 4 weeks, 8 weeks, 12 weeks, and 24 weeks with chest x-rays and USG chest to estimate the level of pleural fluid (resolution/increase in pleural effusion) and pleural thickening (fibrosis/adhesions).



The data collected was compiled and tabulated with help of a Microsoft Excel spreadsheet and analyzed statistically using IBM SPSS Statistics version 25. Descriptive statistics are represented in the form of frequencies on percentage for categorical variables or mean or standard deviation for continuous variables. The association between categorical variables has been assessed by Pearson chi-square test/Fisher test. The p-value of <0.05 is considered statistically significant for purpose of this study.

RESULTS AND DISCUSSION

It was observed that the maximum number of the patients in the study were of middle age with the mean age being 41.60 ± 18.06 years in group I and 37.28 ± 14.83 years in group II with male predominance in both groups. There was no significant difference on the basis of the side involved, the initial size of pleural effusion, or the duration of symptoms with which the patients presented (Table no. 1).

TABLE NO. 1: CLINICAL PARAMETERS OF PATIENTS

Category, variables		Group I (n=50)	Group II (n=50)	p-value
Mean Age ± SD (Years)		41.60 ± 18.06	37.28 ± 14.83	0.507
Gender	Male	37	29	0.091
	Female	13	21	
Duration of Symptoms	≤2 weeks	66%	60%	0.612
	>2weeks	34%	40%	
Side involved	Left	23	27	0.584
	Right	25	20	
	Bilateral	2	3	
Initial Size of Pleural Effusion	Mild	33	30	0.534
	Moderate	17	20	

Subsequently, at 4 weeks, 8 weeks, 12 weeks, and 24 weeks, when compared on the basis of treatment given, it was observed that most of the patients in both groups got relieved of their symptoms in the first 4 weeks of treatment. A similar result has been explained in a study conducted by Estenne M. et al. in which it was mentioned that thoracocentesis led to immediate relief of dyspnea. They concluded that this change with aspiration was due to a decrease in thoracic cage volume allowing the inspiratory muscles to work to full of their advantage as per their length-tension curve [11]. In our study, chest pain was the only symptom that persisted till 12 weeks in both groups [group I (16%) and group II (30%)]. However, it was relieved by the end of 12 weeks with a non-significant p-value. Mathur K.S. et al. observed that fever resolved completely in 5 days with the use of Intrapleural hydrocortisone but it took 40 days in the non-steroid group [12]. Another study conducted by Wyser C. et al. observed that patients got relieved of symptoms by oral prednisolone by the end of 8 weeks which is in accordance with the present study [13]. Engel M.E. et al. in their meta-analysis concluded that there was a shorter duration of the symptomatic period with oral steroids as compared to the non-steroid group [14]. Pleural effusion resolved completely, equally in both groups, with no significant difference (86%-- group I and 96%-- group II). A similar finding of a significant reduction in pleural effusion after 10 days of treatment with oral prednisolone was seen by Mansour A.A. et al. in their study [15]. Even Residual pleural thickening (RPT), at the end of the treatment, was found to be equally present in both groups, with no significant difference (28% group I and 32% group II). In a study done by Sun F. et al., RPT has been seen to be in 48.2% of patients treated with

oral steroids along with ATT [16]. In another study conducted by Menon N.K., it was observed that 34% of cases with intrapleural steroids and 8% of cases with oral steroids showed RPT at the end of treatment [9]. But side effects (nausea, vomiting) were seen more in group I, with a highly significant difference, as compared to group II (Table no. 2). It had already been studied by Mathur K.S. et al. [12] that no significant side effects were seen with intrapleural corticosteroids and studies done by Lee C.H. et al. [17], Wyser C. et al. [13], Bang J.S. et al. [18], Elliott A.M. et al. [19], and meta-analysis by Engel M.E. et al. [14] proved that oral corticosteroids groups showed more side effects. (Table no. 2, chart no. 2).

TABLE NO. 2: OBSERVATIONS DURING/AT THE END OF THE STUDY PERIOD

OBSERVATIONS	OUTCOME	GROUP I	GROUP II	p-value
RESOLUTION OF PLEURAL EFFUSION (AT THE END OF THE STUDY PERIOD)	RESOLVED	86%	96%	3.854
	NOT RESOLVED	14%	4%	
RESIDUAL PLEURAL THICKENING (AT THE END OF THE STUDY PERIOD)	PRESENT	28%	32%	0.663
	ABSENT	72%	68%	
SIDE EFFECTS	SEEN	78%	40%	0.00

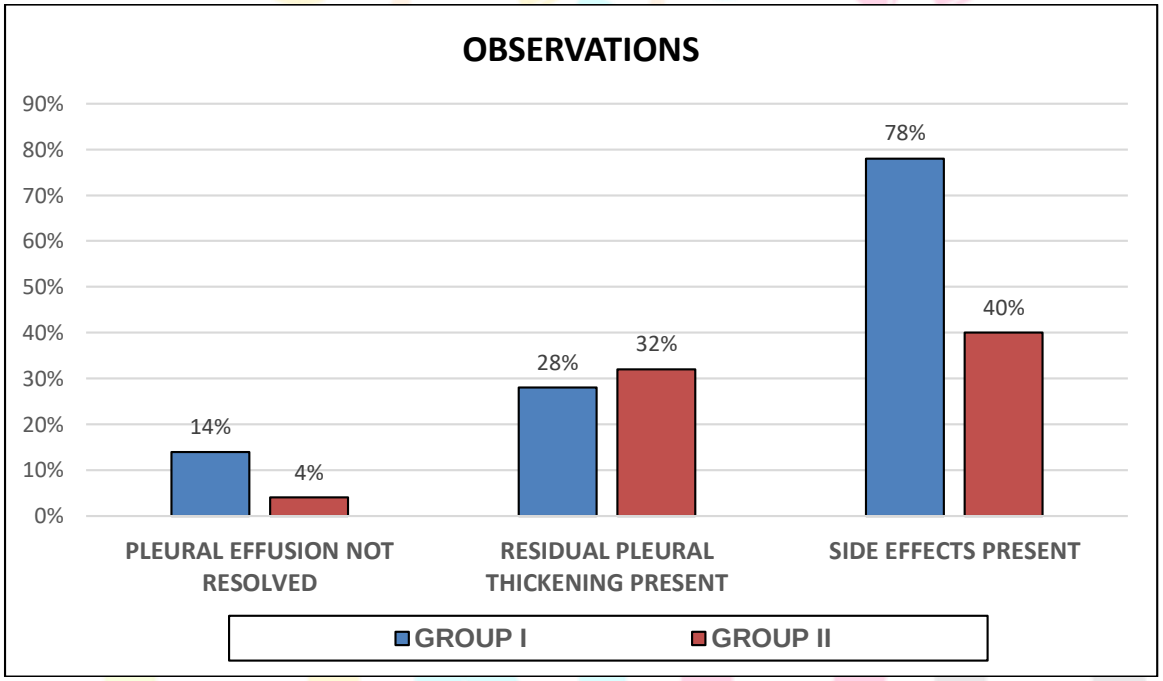


CHART NO. 1: OBSERVATIONS DURING/AT THE END OF THE STUDY PERIOD

CONCLUSION

In the light of above-obtained results, the following conclusion was withdrawn.

Patients of Tubercular Pleural Effusion (TPE) should be started on Anti Tubercular Therapy (ATT) along with steroids as early as possible because a delay in the start of treatment may lead to long-term complications like Residual pleural thickening (RPT). Keeping in view the fewer side effects of local corticosteroids, we also emphasize that Intrapleural corticosteroids should be considered over Oral corticosteroids. Early start of treatment leads to better compliance to therapy which in turn has been shown to correlate with better treatment outcomes and thus prevent complications

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