Original Article

Role of therapeutic thoracentesis in tuberculous pleural effusion

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Abstract:

CONTEXT: Prevalence of tuberculous pleural effusion is very high in the Asian subcontinent but very few studies have come up from this part of the world about the course of recovery of pulmonary functions after institution of anti-tubercular therapy (ATT) and thoracentesis.

AIMS: To study initial lung function impairment, changes over time after institution of ATT and thoracentesis and residual abnormalities left at the end of six months of treatment.

SETTINGS AND DESIGN: Randomized open level interventional study over two years in 52 patients at a tertiary level teaching hospital.

METHODS: The study population was divided into two equal groups, A (therapeutic thoracentesis) and B (diagnostic thoracentesis). Spirometry, chest radiograph and ultrasonography of thorax were done initially and at each follow-up visit up to six months. Statistical analysis was done (P value < 0.05 considered significant).

RESULTS: Both groups were comparable initially. After six months none in group A and five patients in group B had minimal pleural effusion. During follow up, mean percentage predicted of FEV1 and FVC increased more in A than in B and the differences were statistically significant (P < 0.05). Pleural thickening, initially absent in both groups, was found to be more in B as compared to A at subsequent follow-up visits and this was statistically significant (P < 0.05).

CONCLUSIONS: Thoracentesis should be considered in addition to anti-TB treatment, especially in large effusions, in order to relieve dyspnea, avoid possibility of residual pleural thickening and risk of developing restrictive functional impairment.

Key words:
Lung function, residual pleural thickening, thoracentesis, tuberculous pleural effusion

Patients of pleural effusion usually present with dyspnea, chest pain and cough that generally intensify with effort and in many cases interfere with continuation of daily activities.[1] Thoracentesis causes relief of dyspnea and improvement in the mechanical function of the chest, allowing patients to return to their daily activities.[2,3]

Since tuberculosis is the commonest etiology of pleural effusion in our country, the present study was done in patients of tuberculous pleural effusion with the objective of studying the initial lung function impairment, changes over time after the institution of anti-tubercular therapy (ATT) and thoracentesis and the residual abnormalities left at the end of six months of treatment.

Methods

The study was carried out from November 2007 to October 2009 in the department of pulmonary medicine at a tertiary level teaching hospital; the study design being a randomized open label interventional study. All the patients signed an informed consent after the study was approved by the institutional ethics committee.

Patient selection

Patients were enrolled according to the following inclusion criteria: presence of unilateral pleural effusion occupying more than one-half of the hemithorax with an indication for therapeutic thoracentesis. The diagnosis of tuberculous etiology was confirmed by the presence of granuloma in histopathological examination after closed pleural biopsy or demonstration of acid fast bacilli in pleural fluid or biopsy specimens associated with exudative pleural effusion.

Exclusion criteria were as follows: patients with history of smoking; patients with any lung parenchymal lesion as evident by clinical and radiological examinations, e.g. collapse, consolidation, fibrosis or mass with effusion; patients with history of bronchial asthma or chronic obstructive pulmonary disease (COPD); patients with chronic liver or kidney diseases; patients with encysted pleural effusion; patients with any of the conditions which are contraindicated for

spirometry, e.g. recent onset myocardial infarction; patients on oral corticosteroids.

Study procedure

The study population consisted of 52 newly diagnosed cases of unilateral tuberculous pleural effusion. They were divided into two equal groups A and B by assigning every alternate case to each group. All the cases were subjected to detailed clinical examinations, chest radiography (both posterior–anterior and lateral views), color Doppler ultrasonography of thorax to detect the presence or absence of pleural thickening (hypo-echoic area >3 mm in thickness was considered to be thickening of pleura) and spirometry. The patients in group A were subjected to maximal therapeutic thoracentesis and those in group B were subjected to only diagnostic thoracentesis. All the patients in both the groups were initiated on category-I anti-TB regimen under DOTS (Directly Observed Treatment Short-course) as per the Revised National Tuberculosis Control Program (RNTCP). Follow-up of each case was done after first, second and sixth month of ATT. During the follow-up visits, patients were examined clinically and repeat chest radiograph, ultrasonography of thorax and spirometry were done to see any improvement. Any residual lesion or abnormalities observed after completion of ATT were also noted.

Radiography

The pleural fluid on chest radiographs (pre-thoracentesis and post-thoracentesis) was classified as minimal, moderate and massive. Patients with pleural fluid level up to the lower border of fifth rib anteriorly were classified as minimal, up to the lower border of third rib as moderate and above the third rib as massive pleural effusion.[4]

Thoracentesis procedure

Thoracentesis was performed by trained chest physicians using the standard technique, including pleural manometry.[1] The procedure was suspended if spontaneous cessation of fluid drainage occurred or if the patient experienced discomfort with exacerbation of symptoms (coughing, dyspnea or chest pain) or vagal manifestations (dizziness or nausea).

Spirometry

All the patients in the study were evaluated by spirometry. To measure FVC and FEV1, a ZAN 100 pulmonary spirometer (nSpire Health Inc; Longmont, California) was used, and the maneuvers were performed according to the guidelines of the American Thoracic Society and European Respiratory Society.[5]

Statistical analysis

The data were compiled on Microsoft Excel worksheet where proportion and mean values were calculated. Significance of association between two attributes (qualitative data) was analyzed by Chi-square test. Epi-info software (version 3.2) was used to calculate Yates corrected Chi-square and Fischer exact P values in appropriate situations, using 2×2 fourfold tables. The mean values were compared by unpaired Student's t test. One-way repeated measures ANOVA was performed using IBM SPSS software (version 19.0), to compare the mean scores of FEV1, FVC and FEV1/FVC of groups A and B separately on four different occasions viz. before pleural aspiration, one month, 2 months and 6 months after ATT. P value was considered as per Wilks' Lambda statistics. Partial Eta squared, given in the multivariate tests output box was used to represent the change in effect size; value more than 0.14 indicates very large effect size. P value less than 0.05 was considered as statistically significant.

Results

During the study period, 52 patients fulfilled the conditions of the study and they were divided into two groups A and B, having 26 patients each. Males were predominant in both the groups [88.46% (A) and 76.92% (B)] and the difference was statistically insignificant (Chi-square, Fischer exact two tailed $P = 0.46$). Most of the patients in both the groups [53.84% (A) and 61.53% (B)] belonged to the age group of 15 to 35 years. Mean age was 39.03 ± 16.62 years (A) and 33.69 ± 12.05 years (B), respectively, the difference being statistically insignificant (unpaired student's $t = 1.33$, $P = 0.19$). Thus, demographically, both the groups were comparable to each other at baseline.

On chest radiography, 30.77% patients of group A and 26.93% patients of group B had massive pleural effusion, while 69.23% and 73.07% patients of A and B groups, respectively, had moderate pleural effusion before thoracentesis. Initially, none of the patients in either group had minimal pleural effusion. At baseline, both the groups were comparable to each other in terms of the extent of pleural effusion (Yates corrected Chi-square test = 0.00, df = 1, $P > 0.05$). After initiation of treatment, extent of pleural effusion had reduced in both the groups. At one month after ATT and during subsequent follow-up visits, none of the group A patients had either massive or moderate pleural effusion and only 61.54% had minimal pleural effusion. Among group B patients, 15.38% and 84.62% had moderate and minimal pleural effusion, respectively, after one month of treatment and all the patients had minimal pleural effusion as compared to only 26.93% patients of group A at 2 months of treatment. None of the group A patients had any pleural effusion whereas only five patients in group B had minimal pleural effusion after six months of treatment [Table 1].

Regarding spirometry parameters, both the groups were comparable to each other at baseline in terms of mean

Table 1: Extent of tuberculous pleural effusion on chest radiograph (*N* = 52)

Time	Group A extent of pleural effusion			Group B extent of pleural effusion		
	Massive	**Moderate**	**Minimal**	**Massive**	**Moderate**	**Minimal**
Before thoracentesis	8 (30.77%)	18 (69.23%)	0 (0%)	7 (26.93%)	19 (73.07%)	0 (0%)
1 month after ATT	0 (0%)	0 (0%)	16 (61.54%)	0 (0%)	4 (15.38%)	22 (84.62%)
2 months after ATT	0 (0%)	0 (0%)	7 (26.93%)	0 (0%)	0 (0%)	26 (100%)
6 months after ATT	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (19.23%)

ATT = Anti-tubercular therapy, Figures in parenthesis are in percentage

percentage predicted of FEV1 (51.54 vs. 49.19, unpaired student's t test = 0.69, $P = 0.49$), FVC (50.50 vs. 49.23, t test = 0.33, $P = 0.74$) and FEV1/FVC (101.96 vs. 99.96, $t = 1.09$, $P = 0.27$). After thoracentesis during the three different follow-up visits, the percentage predicted of FEV1 and FVC increased in both the groups.

Mean FEV1 value of group A patients increased steadily from 51.54 to 87.62. This increase was statistically significant as evident from Wilks' Lambda = 0.072, F = 99.545, $P < 0.0005$. In group B patients, FEV1 also increased significantly over time [Wilks' Lambda = 0.062, F = 116.13, $P < 0.0005$]. Multivariate partial eta squared suggests a very large effect size in both group A (0.928) and B (0.938) [Figure 1]. At the end of 6 months, FEV1 was significantly higher among group A patients, compared to group B (87.62 vs 84.92, t test = 2.38, $P = 0.02$).

There was also significant increase in mean value of FVC in both the groups [A - Wilks' Lambda = 0.041, F = 179.51, $P < 0.0005$, multivariate partial eta squared = 0.959 vs B - Wilks' Lambda = 0.060, F = 119.20, $P < 0.0005$, multivariate partial eta squared = 0.940] after treatment with a very large effect [Figure 2]. At the end of six months, group A patients had significantly higher FVC as compared to group B patients (86.46 vs. 83.31, t test = 3.28, $P = 0.00$).

However, in both the groups mean score of FEV1/FVC did not change substantially over time as compared to the baseline [In group A: Wilks' Lambda = 0.850, F = 1.351, $P = 0.282$, multivariate partial eta squared = 0.150; In group B: Wilks' Lambda = 0.832, F = 1.551, $P = 0.228$, multivariate partial eta squared = 0.168] [Figure 3].

Before thoracentesis, pleural thickening was absent in both the groups as demonstrated by color Doppler ultrasonography of thorax. Subsequently, at different point of follow-up visits, pleural thickening appeared in both the groups, though the proportion was less in group A as compared to group B and this was statistically significant throughout the three follow-up visits ($P < 0.05$) [Table 2].

Discussion

Tuberculous pleural effusion is the second most common form of extra pulmonary TB, only less frequent than lymph node TB. This is particularly important in the present era of human immunodeficiency virus (HIV) infection, when extra pulmonary TB is more commonly encountered in clinical practice.[6] Majority of patients with TB live in the most populous countries of Asian subcontinent, which accounts for nearly half of the new cases that arise yearly.[7] In our country, where about 40% of the population is infected with the TB bacillus and

which accounts for a fifth of the global burden of tuberculosis,[8] priority of our National TB control program has always been given to the sputum smear positive pulmonary TB cases and there is a lack of data on the incidence of extrapulmonary TB patients. Thoracentesis is one of the commonest procedures done in hospital settings in our country but there are very few studies from this part of the world on the effect of thoracentesis in patients of tuberculous pleural effusion.
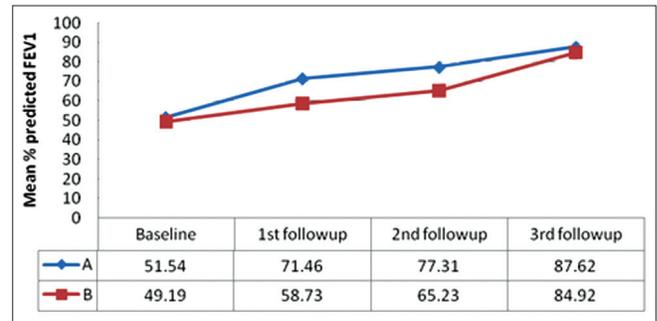

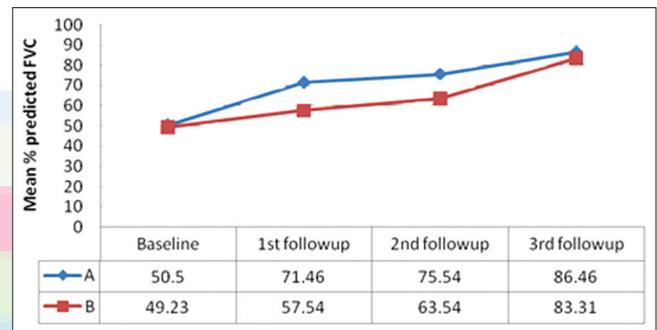**Figure 1:** Line diagram showing mean % predicted FEV1 in both the groups at baseline and follow-up visits

	Baseline	1st followup	2nd followup	3rd followup
A	51.54	71.46	77.31	87.62
B	49.19	58.73	65.23	84.92

Figure 2: Line diagram showing mean % predicted FVC in both the groups at baseline and follow-up visits

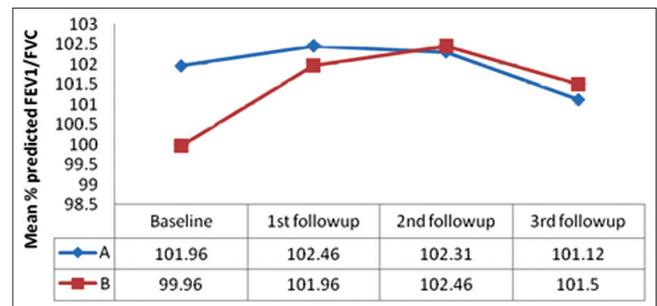|	Baseline	1st followup	2nd followup	3rd followup
A	50.5	71.46	75.54	86.46
B	49.23	57.54	63.54	83.31

Figure 3: Line diagram showing mean % predicted FEV1/FVC in both the groups at baseline and follow-up visits

	Baseline	1st followup	2nd followup	3rd followup
A	101.96	102.46	102.31	101.12
B	99.96	101.96	102.46	101.5

Table 2: Residual pleural thickening in tuberculous pleural effusion ($N = 52$)

Time	Group A pleural thickening		Group B pleural thickening		Statistical test Chi-square test (Yates corrected), df, P value
	Present	Absent	Present	Absent	
Before thoracentesis	0 (0%)	26 (100%)	0 (0%)	26 (100%)	--
1 month after ATT	7 (26.93%)	19 (73.07%)	24 (92.31%)	2 (7.69%)	20.45, 1, 0.00
2 months after ATT	7 (26.93%)	19 (73.07%)	23 (88.46%)	3 (11.54%)	17.73, 1, 0.00
6 months after ATT	3 (11.54%)	23 (88.46%)	11 (42.30%)	15 (57.70%)	4.79, 1, 0.02

ATT = Anti-tubercular therapy, Figures in parenthesis are in percentage

Our study on a series of patients of tuberculous pleural effusion showed male preponderance and most of the patients were in the age group of 15–35 years. Similar age and sex distribution was also found by Singla R in his study.[4] In general, patients with tuberculous pleural effusion are found to be younger than patients with parenchymal TB. The high male preponderance may be due to the prevailing socio-economic conditions and health-seeking behavior of the patients in our country.

All the patients included in our study had moderate to massive pleural effusion and experienced dyspnea at rest or on exertion. Patients in group A, who underwent therapeutic thoracentesis, had immediate relief from dyspnea after drainage of pleural fluid whereas those in group B had a gradual relief from dyspnea. We did not include any objective tool like visual analogue scale or the Borg score to demonstrate the effect of thoracentesis on dyspnea. However, there was significant subjective clinical improvement in all the patients that underwent therapeutic drainage of pleural fluid. We speculate that the subjective improvement was perhaps related to altered nervous impulses from the lung or the chest wall. Estenne *et al*.[9] suggested that the relief of dyspnea after thoracentesis resulted primarily from reduction in size of the thoracic cage, which allowed the inspiratory muscles to operate on a more advantageous portion of their length–tension curve. Ana Maria *et al*.[10] had demonstrated in their study that therapeutic thoracentesis relieves dyspnea not only at rest but also on exertion, improves six-minute walk test and allows quick and better re-adaptation of patients to routine activities. Feller-Kopman *et al*.[11] had also suggested draining the pleural space completely.

As in previous studies, we had shown that pleural effusion was associated with restrictive ventilatory impairment. The spirometry parameters before thoracentesis were comparable in both the groups of patients. There were significant improvements in FEV1 and FVC over the study period of six months in both the groups but the patients who underwent therapeutic thoracentesis had significantly higher improvements than those without therapeutic thoracentesis. However, there was no statistically significant change in FEV1/FVC after six months of treatment. Prior studies demonstrated that immediately after thoracentesis, the spirometry variables improved.[9,12-14] Initial significant impact with an improvement of >10% in both FEV1 and FVC has been reported. However, it should be noted that this improvement was observed immediately or 24 hours after thoracentesis, when the adjustment of the respiratory system to this new condition may not have occurred yet. Some previous studies have also shown that there is no improvement[12,15] or a relatively small improvement[9,16] in pulmonary function and arterial blood oxygenation following therapeutic thoracentesis. Results similar to that of our study were also reported by Singla,[4] Bhatia *et al*.[17] and Wang *et al*.[18] in their studies on pleural effusion. Impairing full expansion of the ipsilateral lung as well as impedance of expansion of contralateral lung in cases with mediastinal shift and relative distension of the ipsilateral chest wall could be suggested as underlying mechanisms for restrictive pattern observed in patients with pleural effusion.[19,20] Therefore, alleviation of these mechanical effects of pleural effusion by aspiration of pleural fluid might explain the significant improvements in spirometry parameters in our study.

The number of patients with residual pleural thickening was less after therapeutic thoracentesis in our study and this was statistically significant ($P < 0.05$). It has been estimated that up to 50% of tuberculous pleural effusions develop pleural thickening[21] and such development can cause restrictive lung impairment. Therapeutic thoracentesis is thought to reduce such incidence by facilitating a more complete drainage of effusion, thereby reducing the amount of inflammatory exudate in the pleural space and causing less fibrin formation and deposition.[22-24] However, many recent studies have concluded that therapeutic thoracentesis has no additional benefit over standard anti-TB treatment and the development of residual pleural thickening does not appear to be influenced by such intervention.[25-27]

There had been some limitations of our study. The detection of pleural thickening was done by ultrasonography of thorax and there could have been some bias or inter-observer variations among the radiologists. Secondly, we did not assess the patients with pleural thickening beyond six months. Thirdly, we did not include any tool for objective assessment of improvement in dyspnea.

The obvious implication of our study is that thoracentesis should be considered in addition to standardized anti-TB treatment, especially if they are large, in order to relieve dyspnea, to hasten the resolution of pleural effusion, to accelerate the recovery of pulmonary function, to avoid the possibility of healing with pleural thickening and its risk of developing restrictive functional impairment. This rationale may be viewed with some skepticism in view of some recent contradictory evidence. Our findings also add to the existing evidence that directly observed intermittent anti-TB treatment is effective in tuberculous pleural effusion in the context of a resource poor setting.[28] We believe our findings are useful in practicing evidence-based medicine and provide preliminary benchmark data for further larger prospective studies in our country with a huge burden of tuberculosis.

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