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Study to Evaluate the Role of Single Intrapleural Steroid Instillation in Improving Outcome in Patients of Tubercular Pleural Effusions Receiving Standard Anti Tubercular Treatment

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ABSTRACT *The pleural inflammatory reaction in TB results in long term restricted lung function after the standard ATT in a significant proportion of observed cases. Research findings about benefit of use of oral corticosteroids are inconsistent. There is only one study on intrapleural corticosteroid instillation. 114 adult patients with simple tuberculous pleural effusions received single intrapleural hydrocortisone succinate 100 mg dose with standard ATT. Their outcome was compared with a control group of 120 patients receiving standard ATT, in terms of improvement in CXR, USG, dyspnoea scores and spirometry at the end of 2 and 6 months. The study group showed statistically significant improvement in all these outcome parameters as compared with the control group.*

Review of Literature and importance of the study
In many regions of the world where TB is more common, TB pleural effusion maintains its position as the leading inflammatory pleural disease (1, 2). In fact, pleural disease is one of the most common extra-pulmonary involvement in TB in developing countries (3, 4). The effusion is secondary to the rupture of a subpleural caseous focus in the lung into the pleural space. Delayed hypersensitivity plays an important role in the development of the TB pleural effusion(4). The intense inflammatory reaction obstructs the lymphatic pores in the pleura, causing proteins to accumulate in the pleural space with subsequent retention of fluid(5,6). This results in impaired lung inflation and leads to restriction of lung function in the long term. Despite successful completion of standard anti-tuberculous medication, nearly 10% patients may have a residual restrictive ventilatory defect on spirometry (7). Mild degree of pleural fibrosis may be observed on chest radiographs a year after therapy is begun in up to 50% patients (8). A faster resolution of pleural effusion during the initial phase of treatment may decrease the occurrence of significant pleural thickening (9). Some clinicians believe that corticosteroids used in combination with anti-tuberculous drugs can help to prevent these complications (9).

Some found no clear evidence (10, 12) supporting the use of corticosteroids in people with tuberculous pleural effusion. The use of corticosteroids may relieve symptoms more rapidly and increase absorption of pleural effusion (11), but the occurrence of pleural adhesion has not been shown to be influenced by the administration of corticosteroids. Some authors suggested that in the absence of contraindications, corticosteroids should be routinely prescribed with ATT in TB pleural effusion (13). Some others say this is unnecessary and has no long-term benefit.

All above literature has considered the role of oral corticosteroids.

This study was carried out to study the effectiveness of single intrapleural instillation of hydrocortisone in hastening resorption of fluid and in reducing loculations and residual pleural thickening.

The action of intrapleural hydrocortisone seems to be solely at the tissue level by virtue of its anti-inflammatory and anti-exudative properties.There has been only one study on intrapleural instillation of corticosteroids in tuberculous pleural effusions; it involved multiple instillations in a single patient. (14).

Drugs instilled intrapleurally are known to reach systemic circulation in high concentrations(15). Hence, the dose of hydrocortisone used is not greater than any single dose used safely by intravenous route.

There was a significant association between MRC grade and exercise performance, SGRQ, depression score and age. Spirometric readings were not associated with MRC grade (16) in COPD patients.

Materials & Methodology :
Institutional ethical clearance was obtained. From among those attending the Pulmonary Medicine department of a tertiary care teaching institute (Smt Kashibai Navale Medical College & General Hospitals) in Pune during the period April 2011 to Dec 2012, patients with simple, Tubercular pleural effusions were enrolled after taking informed written consent.

Patients with loculated effusions and/or pleural thickening ,effusions of non-tubercular etiologies, empyema and HIV positives were not enrolled. If patients had contraindications to use of hydrocortisone or to ATT or had co-morbid illnesses, they were excluded from the study.

Adult patients of either gender with diagnosed Tuberculous Pleural Effusions were randomized into study and control groups. The diagnosis of tuberculous pleural effusion was based on the clinical presentation (symptoms, clinical find-

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ings), CXR, a positive tuberculin test and pleural fluid characteristics (lymphocytosis , increased protein content and ADA levels above 40 IU/L).

Both groups received ATT as per RNTCP Guidelines [$2(HRZE)_3/4(HR)_3$] and therapeutic aspiration. In the study group, 200 mg. of hydrocortisone succinate was injected into the pleural cavity only once at the end of therapeutic aspiration. None of the patients received oral steroids or any other medication. Every patient in both groups was encouraged to do deep breathing exercises under the guidance of the physiotherapist.

MMRC Dyspnoea score, Chest X Ray, USG Thorax and spirometry were recorded at 0, 2, and 6 months. Evaluation of the effect of the intrapleural hydrocortisone instillation was made on the basis of dyspnoea score, X ray chest, USG thorax (fluid, loculation, pleural thickening) and Spirometry at 2 and 6 months. At the end of the study, we had complete data of 234 patients (114 and 120 in the study and control groups respectively), for analysis.

Chi square test and unpaired t test were used to find association. P value of less than 0.05 was considered as statistically significant. Epi Info ™ 7.1.2 software dated 07/04/2013 was used for analysis purpose.

Observations

All patients whose data has been taken for analysis have responded well to standard ATT. No adverse effects to the intrapleural intervention were observed in either group.

The gender - age group distribution and baseline Chest X Ray grading did not show significant difference; hence, the study and control groups were comparable at the start of the study as per Table 1 below.

Variable	Study grp n=114	Control grp n=120	Chi square value	Degree of freedom	P value	Significant
Gender : male	76	86	0.6861	1	0.4074	No
Gender : female	38	34				
Age grp* Very Young	30	38	1.3912	3	0.7076	No
Age grp* Young	36	32				
Age grp* Middle aged	30	34				
Age grp* Old	18	16				
CXR** : Minimal	28	30	0.069	2	0.9661	No
CXR** : Moderate	50	54				
CXR** : Massive	36	36				

*** Age groups : 18 – 25 very young; 26 – 40 young ; 41 – 55 middle aged ; >55 old**

**** Chest X Ray : above 4th rib massive; 4th to 6th ribs moderate; below 6th rib minimal**

Within each group, females constituted one third of the total patients.

There were almost equal number of patients in the very young, young and middle aged groups; old patients were half the number in any of the other age groups.

Most of them were moderate pleural effusions.

Table 2: at the end of 2 months

Feature	Study group	Control group	Chi square value	Deg of freedom	P value	Significant
CXR : Minimal	86	86	13.153	2	0.0014	yes
CXR : Moderate	4	20				
CXR : Massive	24	14				
Loculation present	6	32	19.689	1	0.0000001	Yes
Loculation absent	108	88				
Pl thickening# present	12	102	34.3103	1	0.0000001	Yes
Pl thickening# absent	54	66				
No** improvement in MMRC	2	8	X^2=65.013	2	0.000001	Yes
Mild** improvement in MMRC	16	51				
Moderate** improvement in MMRC	18	41				
Massive** improvement in MMRC	78	20				

 # Pleural thickening: present when > 3mm as measured on USG.

****No improvement and mild improvement were clubbed for analysis purpose. Grading of MMRC dyspnoea score improvement : Mild : 1; moderate : of 2 or 3; massive : of 4 or 5**

Table 3 : at the end of 6 months

Feature	Study group	Control group	Chi square value	Deg of freedom	P value	Significant
CXR : Minimal	52	58	0.1735	1	0.6769	No
CXR : normal	62	62				
Loculation present	6	28	15.371	1	0.000008	Yes
Loculation absent	108	92				
Pl thickening# present	12	102	37.039	1	0.0000001	Yes
Pl thickening# absent	54	64				
No** improvement in MMRC	0	4	X^2=29.503	2	0.000001	Yes
Mild** improvement in MMRC	4	22				
Moderate** improvement in MMRC	20	38				
Massive** improvement in MMRC	90	56				

Tables 2 and 3 above show significant improvement in USG and MMRC dyspnoea scores in the study group as compared to the control group at the end of 2 and 6 months.

Volume : 3 | Issue : 10 | Oct 2013 | ISSN - 2249-555X

Table 4 : FVC* and FEV1/FVC* ratio

Improvement in	Frequency	Mean	S.D.	d.f.	P value	Statistically significant
FVC at 2 months : study grp	114	9.904	6.298	232	0.002	yes
FVC at 2 months : Control grp	120	7.367	5.915			
FVC at 6 months : study grp	114	14.11	8.764	232	0.00001	yes
FVC at 6 months : Control grp	120	9.95	7.284			
FEV1/FVC at 2 mths : study grp	114	7.956	3.9	232	0.00001	yes
FEV1/FVC at 2 mths : Control grp	120	5.8	2.452			
FEV1/FVC at 6 mths : study grp	114	11.38	4.911	232	0.00001	yes
FEV1/FVC at 6 mths : Control grp	120	9.167	3.654			
FVC at 2 mths: study grp	114	72.3860	3.7899	232	0.00001	yes
FVC 2 mths:Control grp	120	69.35	3.9186			
FVC at 6 mths:study grp	114	76.5614	3.7156	232	0.00001	yes
FVC 6 mths:Control grp	120	71.8833	3.9624			
FEV1/FVC ratio at 2 mths : study grp	114	82.4912	2.6281	232	0.00001	yes
FEV1/FVC ratio at 2 mths : Control grp	120	84.5833	3.4655			
FEV1/FVC ratio at 6 mths : study grp	114	78.9649	2.1938	232	0.00001	yes
FEV1/FVC ratio at 6 mths : Control grp	120	81.2167	4.0712			

***FEV1 has been recorded as % of predicted .The improvement is recorded as improvement in this %.**
**** FEV1/FVC ratio before treatment minus FEV1/FVC ratio after treatment is recorded as the improvement in the ratio.**

The improvement in FVC in the study group patients was significantly more than control group patients at both 2 and 6 months.

The improvement in FEV1/FVC ratio in the study group patients was significantly more than control group patients at both 2 and 6 months.

Conclusions :
Single Intrapleural instillation of Hydrocortisone succinate in simple Tuberculous pleural effusions helps faster improvement in symptoms like dyspnoea score , lower incidence of loculation and residual pleural thickening and better improvement in lung functions.

We have not directly studied the symptomatic improvement (fever, chest pain, cough, anorexia, malaise). More studies should be taken up with bigger sample size and longer follow up duration to further evaluate the findings of this study.

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