Original Article

# Pulmonary Rehabilitation in Patients with Interstitial Lung Diseases in an Outpatient Setting: A Randomised Controlled Trial

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**Abstract**

**Background.** Interstitial lung diseases (ILDs) are a group of progressive diseases with few effective treatments. Pulmonary rehabilitation is a non-pharmacological intervention with a proven role in COPD. However, there is limited evidence on its usefulness in patients with ILDs.

**Objectives.** This study was planned to assess the effect of pulmonary rehabilitation on exercise capacity and health-related quality-of-life (HRQoL) in patients with ILD.

**Methods.** Forty patients with stable ILDs were randomised to receive either conventional treatment (control group) or standard treatment plus pulmonary rehabilitation programme for 8 weeks (study group). Exercise capacity was assessed by six-minute walk test (6MWT) and QoL was measured by St George's Respiratory Questionnaire (SGRQ) at baseline and at the end of 8 weeks.

**Results.** At the end of 8 weeks, there was a statistically significant improvement in 6MWT distance (mean increase of 23.8 meters; p=0.037) and a significant decline in the SGRQ score (by 8.8 units; p=0.003) in the study group as compared to the control group.

**Conclusion.** Pulmonary rehabilitation improves exercise capacity and HRQoL in patients with stable ILDs.
**[Indian J Chest Dis Allied Sci 2017;59:75-80]**

**Key words:** Interstitial lung disease, Pulmonary rehabilitation, Six-minute walk test.

## Introduction

Interstitial lung disease (ILD) is a diverse group of over 200 disorders characterised by varying degrees of inflammation and fibrosis of pulmonary interstitium. These diseases have a chronic and usually progressive course heralding poor outcome. Symptoms may vary from asymptomatic state to progressive breathlessness and dry cough, finally resulting in chronic respiratory failure. Once considered rare, it is now being increasingly reported from various parts of the world.[1]

Anti-inflammatory agents, like steroids and immunosuppressive therapies are often used to treat the patients with ILDs, however, their use is accompanied by significant side effects. Apart from a limited role in certain ILDs, these have not been shown to retard disease progression or impart a survival benefit in idiopathic pulmonary fibrosis (IPF).[2] Recently, pirfenidone, an anti-fibrotic agent, has yielded promising results in patients with IPF by retarding the disease progression.[3] However, significant number of ILD patients present in advanced stage of the disease with extensive fibrosis, when pharmacological treatment is of little use. With progression of the fibrosis, these patients restrict their daily activities that leads further to muscular and cardiovascular deconditioning. Worsening symptoms along with decreased functional capacity lead to impairment in health-related quality-of-life (HRQoL).[4] Hence, pulmonary rehabilitation (PR) is a potential treatment option that might limit or improve the symptoms associated with the disease.

As per the 2013 American Thoracic Society/ European Respiratory Society (ATS/ERS) Statement, "pulmonary rehabilitation is a comprehensive intervention based on a thorough assessment of the patient followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behaviour change, designed to improve the physical and emotional condition of patients with chronic respiratory diseases and to promote the long-term adherence to health-enhancing behaviours.[5,6] Most of the evidences supporting the effectiveness of PR has come from studies on patient with chronic obstructive pulmonary disease (COPD). Pulmonary rehabilitation has been shown to improve exercise endurance, control dyspnoea and improve HRQoL in patients with COPD.[5,7,8]

**[Received: July 27, 2016; accepted after revision: November 9, 2016]**

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The ATS/ERS consensus report supports the use of PR in the management of chronic respiratory diseases regardless of the underlying disease.[5] However, data supporting the use of PR in ILDs is scarce, with the available literature showing favourable results. [9,10] The present study was designed to evaluate the effects of PR on exercise capacity, dyspnoea and HRQoL of Indian patients with ILDs.

## Material and Methods

This was a randomised, controlled trial conducted on stable ILD patients attending Pulmonary Medicine out-patient department of Government Medical College Hospital (GMCH), Chandigarh between September 2012 and September 2014. Diagnosis of ILD was made in accordance with the accepted criteria based on comprehensive evaluation of the clinical, radiological and histopathological features and guided by the serological studies, wherever necessary.[11] Every effort was made to categorise ILD into specific aetiological types, like IPF, non-IPF, idiopathic interstitial pneumonia (IIP), connective tissue disease related ILD, sarcoidosis, etc. Based on the results from a previous study,[12] anticipating a mean increase in six-minute walk test (6MWT) distance of 46 metres in patients with ILD undergoing PR as compared to controls at 5% level of significance and 80% power, the required sample size was calculated as 40 subjects. The study protocol was approved by the Institutional Ethics Committee.

Patients with acute exacerbation of IPF, severely ill patients with intractable breathlessness at rest or on home oxygen therapy, unstable cardiovascular disease (unstable angina or recent myocardial infarction) and disabling arthritis were excluded from the study.

After obtaining an informed written consent, patients were randomised by permuted block randomisation using a block size of 4 into 2 groups of 20 patients each, 'study group' receiving PR along with conventional treatment and 'control group' receiving conventional treatment alone.

A detailed medical history along with general physical and systemic examination data was obtained for each patient. Spirometry test was performed following recommended guidelines.[13] Dyspnoea was scored using the Medical Research Council (MRC) dyspnoea scale.[14]

The HRQoL was assessed by St. George's Respiratory Questionnaire (SGRQ, version- 2.3). Responses to its 50 items were aggregated into an overall score as well as divided into 3 sub-scores, viz, symptom score, activity score and impact score. A change of four units or more in the overall score was considered clinically significant.[15]

Exercise capacity was assessed by six-minute walk test (6MWT) performed as per recommended guidelines.[16] The test measures the distance that a patient can walk at their own pace on a flat hard surface in a period of six minutes. Each patient was explained about the procedure prior to the test. The test was performed on a hospital hall-way measuring 100 feet in length. Supplemental oxygen was provided during the test, if needed.

All the above measurements were taken at baseline and at the end of 8 weeks. Non-attendance within 3 weeks of the stipulated follow-up time was considered as failure to attend.

### *Pulmonary Rehabilitation*

Patients in the study group received PR for a total duration of 8 weeks. Components of PR consisted of patient assessment, exercise training, education, nutrition and psycho-social rehabilitation. The patients were educated about the disease, drugs used in the treatment, behavioural modification and non-pharmacological treatment modalities. Exercise training was given in four sessions per week, of which two were conducted under supervision at the PR centre at our hospital. Each session lasted for upto two hours with adequate rest in between, as required. Each supervised exercise session consisted of endurance and strength training of lower and upper limb muscles as well as inspiratory muscle training. To accomplish this, different methods of exercise were used, like cycle ergometry, walking, aerobic exercises, weight lifting for upper limb muscles, squats, leg press, straight leg raising, stair climbing, etc. Ventilation muscle training was performed by doing different breathing techniques and using flow resistive devices. Exercise was stopped if the arterial oxygen saturation ($SpO_2$) fell below 88% or when patient could not tolerate the exercise. Requirement for supplemental oxygen was assessed on an individual basis so as to maintain a $SpO_2$>90%. Patients were also instructed to record their home exercise in a diary, which was reviewed every week.

### *Statistical Analysis*

Discrete categorical data are presented as number (n) (%); continuous data are presented as mean ± SD and median. Normality of quantitative data was checked by means of Kolmogorov Smirnov test. Mann-Whitney U-test was used for comparing skewed continuous variables. Paired and unpaired t-tests were used to compare continuous variables within each group and between trial arms, respectively. All statistical tests were two-tailed; a p-value less than 0.05 was considered significant. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) for Windows (version 15.0; SPSS Inc., Chicago, IL, USA).

## Results

A total of 40 patients with ILD were enrolled in the study (Table 1). The mean age, gender distribution and BMI of patients in study and control groups were found to be similar. IPF was the most common type of ILD in the present study (62.5%) (Table 2).

**Table 1. Baseline characteristics of the patients with interstitial lung diseases**

| Characteristics | Study Group (n=20) | Control Group (n=20) | p value |
|---|---|---|---|
| **Mean age ±SD (years)** | 59.1±10.4 | 62.10±14.5 | 0.46 |
| **Gender** | | | |
| Male | 8 | 8 | 0.62 |
| Female | 12 | 12 | |
| **No. of Smokers** | 8 | 6 | 0.72 |
| **BMI (±SD)** | 23.8±4.5 | 23.0±2.7 | 0.51 |
| **FVC (% predicted)** | 52.4±13.7 | 58.6±13.7 | 0.21 |

***Definition of abbreviations:*** SD=Standard deviation; BMI=Body mass index; FVC=Forced vital capacity

**Table 2. Distribution of ILD between study and control groups**

| Disease Distribution | Study Group | Control Group |
|---|---|---|
| IPF | 12 | 13 |
| RB-ILD | 1 | 1 |
| COP/BOOP | 1 | 0 |
| Sarcoidosis | 1 | 2 |
| NSIP | 1 | 1 |
| CTD related ILD | 2 | 1 |
| Radiation induced ILD | 1 | 1 |
| Unspecified | 1 | 1 |
| **Total** | **20** | **20** |

***Definition of abbreviations:*** ILD=Interstitial lung disease; IPF=Idiopathic pulmonary fibrosis; RB-ILD=Respiratory bronchiolitis-ILD; COP=Cor-pulmonale; BOOP=Bronchiolitis obliterans organising pneumonia; NSIP=Non-specific interstitial pneumonia; CTD=Connective tissue disorder

The 6MWT distance in the study group and controls were comparable at baseline (237.4±90.4 m *versus* 208±93.7 m respectively). After 8 weeks of PR, 6MWT distance in the study group significantly improved to 261.2±113.1 meters (p=0.003) while change in the control group was not statistically significant (p=0.617) (Table 3). The improvement in the study group was statistically significant as compared to the control group (p=0.037).

**Table 3. Comparison of 6MWT distance between study and control group**

| | Baseline 6MWT Distance (in meters) | 6MWT Distance after 8 Weeks (in meters) | Mean Difference (in meters) | p value |
|---|---|---|---|---|
| Study group | 237.4±90.4 | 261.2±113.1 | 27±30.8 | 0.003 |
| Control group | 208±93.7 | 211.4±108.8 | 3.2±29.1 | 0.617 |

The mean SGRQ score in the study group at baseline was 61.2±14.3 and it decreased to 52.3±17.4 at the end of 8 weeks after PR. The improvement was statistically significant (p=0.001). However, SGRQ score did not improve in the control group. There was a significant decline in the mean SGRQ score of 8.8 units with PR as compared to control group at the end of 8 weeks (p=0.003) (Table 4).

**Table 4. Comparison of SGRQ scores between study and control group**

| | Baseline SGRQ Score | SGRQ Score after 8 Weeks | Mean Difference | p value |
|---|---|---|---|---|
| Study group | 61.2±14.23 | 52.3±17.4 | -8.89±3.6 | 0.001 |
| Control group | 56.7±17.4 | 56.2±17.4 | -0.47±7.6 | 0.492 |

Eighty percent of patients in the study group achieved a minimally clinically important difference (MCID) of 4 or more in SGRQ as compared to 40% of controls (p=0.022). On further analysis, it was seen that the change in impact score and activity score in the study group was statistically significant as compared to the controls (p=0.029 and p<0.001, respectively). However, symptom score did not show any significant improvement in study group after PR (p=0.498).

The MRC dyspnoea scale did not show a significant improvement in study group compared to the controls. However, on within the group analysis it was statistically significant in the PR group (p=0.01). Lung function parameters, particularly forced vital capacity (FVC), showed no improvement in either groups (Table 5).

**Table 5. Comparison of forced vital capacity between study and control group**

| | Forced Vital Capacity (% predicted) | | |
|---|---|---|---|
| | **Baseline** | **After 8 weeks** | **p value** |
| **Study group** | 52.45±13.77 | 53.05±11.07 | 0.68 |
| **Control group** | 58.65±13.75 | 59.15±15.21 | 0.779 |

## Discussion

We assessed the impact of outpatient PR programme in patients with ILDs and observed significant improvement in exercise capacity and HRQoL in patients with ILDs following PR for 8 weeks. To the best of our knowledge, this is the first randomised, controlled study to evaluate the role of PR in ILDs from Indian setting.

Idiopathic pulmonary fibrosis comprised the maximum number of the ILD patients in both the groups. Considering the fact that ILDs are a heterogenous group of diseases with diverse aetiologies, predominance of one ILD over the other may vary, depending on geographical/environmental factors. The patients had a mean age of 60 years which was similar to other studies.[11,17-20]

In this trial, we found a mean improvement of 23.8 meters in 6MWT distance after PR which is statistically significant on intra- as well as inter-group analysis. However, the clinical value of this improvement cannot be interpreted as the minimum clinically important difference (MCID) for 6MWT distance in ILDs is still under debate. In a large cohort of 822 IPF patients, the MCID for the 6MWT distance was projected to be 24–45 meters.[21] A Cochrane systematic review published in 2014, evaluating 9 studies, found an improvement of 44.3 meters in 6MWT in patients with ILD after PR.[21] A few recent studies[11,17,18] have shown a higher improvement in 6MWT in the range of 46-61 meters (Table 6). The higher values could be due to inclusion of patients with less severe disease and bigger sample size in these studies. In contrast, Kozu *et al*[22] found an increase of only 16 meters in the 6MWT distance in 36 patients with IPF.

In the present study, we found a significant improvement in HRQoL in ILD patients after 8 weeks of PR. In a randomised controlled trial, Nishiyama *et al*[11] also assessed the effect of 8 weeks of PR on SGRQ score in ILD patients and their results were comparable to that of the present study (Table 6). Eighty percent of patients in the study group in the present study achieved the MCID of 4 or more points.[23] However, MCID of 4 points in the SGRQ score has been validated in patients with COPD only. Therefore, the exact MCID in patients with ILD needs to be evaluated. Nevertheless, significant improvements seen in SGRQ and 6MWT distance in our study as well as safety in performing the procedures is encouraging enough to advocate the use of PR in the management of patients with ILDs.

**Table 6. Comparison of results with recently published studies**

| | **Holland *et al*[9] (2008)** | **Nishiyama *et al*[17] (2008)** | **Ferrreira *et al*[10] (2009)** | **Swigris *et al*[18] (2011)** | **Huppman *et al*[16] (2013)** | **Present study** |
|---|---|---|---|---|---|---|
| Number of subjects | 57 | 28 | 99 | 21 | 402 | 40 |
| Type of study | RCT | RCT | Uncontrolled Retrospective cohort | non-randomised | Prospective | RCT |
| Type of patients | Outpatient | Outpatient | Outpatient | Outpatient | Inpatient | Outpatient |
| Mean age (years) | 67 | 68+9 | 66 | 71.5±7.4 | 60±1 | 60.8 |
| ILD group | ILD | IPF only | ILD | IPF only | ILD | ILD |
| Duration of PR | 8 weeks | 8 weeks | 6-8 weeks | 6 weeks | 30 days | 8 weeks |
| Change in 6MWT distance (meters) | 35 | 46 | 56 | 61 | 46 | 23.8 |
| Health related quality of life (tool used and response to PR) | CDRQ Improved | SGRQ Improved | USCD questionnaire; Improved | SF-36 Not Improved | SF-36 Improved | SGRQ Improved |
| FVC (%predicted) | No change | No change | – | No change | Improved | No change |
| Dyspnoea (scale used and the response to PR) | MRC Improved | BDI Not improved | Borg score Improved | – | VAS Not improved | Insignificant improvement |

***Definition of abbreviations:*** RCT=Randomised controlled trial; ILD=Interstitial lung disease; IPF=Idiopathic pulmonary fibrosis; PR=Pulmonary rehabilitation; 6MWT=Six-minute walk test; CDRQ=Chronic Disease Respiratory Questionnaire; SGRQ=St George's Respiratory Questionnaire; USCD=University of California San Diego; SF-36=Short form-36; FVC=Forced vital capacity; MRC=Medical Research Council; BDI=Breathlessness dyspnoea index; VAS=Visual analogue scale.

On component analysis of SGRQ, it was found that the symptom-score did not improve significantly as compared to the impact and activity scores in the study group. This finding, also seen in a previously published study[24], could be due to the fact that SGRQ score contains questions on cough, expectoration, wheezing etc which are more pertinent to airway disease, like COPD. There is a need to design a better tool for evaluating HRQoL in patients with ILD. Overall, HRQoL improves in patients with ILD following PR, because the education and exercise programme helps them cope up with the disease, mitigates anxiety and boosts their functional capacity but without any improvement in blood oxygen level.

We also observed small but statistically significant improvement in dyspnoea score in patients undergoing PR. However, it was not evident on between-group analysis. We speculate that ILD patients walking at their highest possible capacities achieve their dyspnoea threshold more rapidly, in contrast to COPD patients, independent of the distance walked. Published data on the effect of PR on dyspnoea in ILDs is conflicting,[24] and hence, no definite conclusion can be drawn with the available data. In the present study, baseline dyspnoea score was also seen as a factor predicting improvement in 6MWT distance and SGRQ score. Patients with grade IV dyspnoea scale showed significant improvement in 6MWT distance and SGRQ score. This was in contrast to study by Kozu *et al*[22] in which patients with grade 2 and 3 dyspnoea scale showed improvement in 6MWT.

Lung function tests constitute important parameters to evaluate functional improvement in any chronic respiratory disorder. However, our study did not show statistically significant improvement in FVC. The results are similar to previous studies[9,11,18] though these studies enrolled only IPF patients for evaluation. It seems that PR improves the muscle strength in patients with ILD without reversing the basic pathology, i.e. interstitial fibrosis. Improvement in muscle strength translates into improvement in exercise capacity rather than lung function parameters.

No adverse effects associated with PR were seen in the present study. Our study has some limitations. Patients with ILD of different aetiologies were enrolled, thus, giving a comprehensive picture of the benefit of PR in ILD. However, the small sample size might hinder the applicability of the results to all ILD patients. Due to the small number of patients, subgroup analysis to evaluate the effect of pulmonary hypertension and long-term oxygen therapy (LTOT) on the outcome, could not be done. It was a non-blinded trial due to obvious reasons. The study did not follow patients beyond 8 weeks to see the long-term effects of pulmonary rehabilitation.

## Conclusions

We found that pulmonary rehabilitation is a safe option for patients with interstitial lung diseases besides medication, as pulmonary rehabilitation helps in improvement in the functional exercise capacity and health-related quality-of-life. It seems justified to include pulmonary rehabilitation in the standard management of patients with interstitial lung diseases. However, larger studies are required to assess the long-term benefits of pulmonary rehabilitation and to determine the predictors of improvement. Future research should also focus on devising optimum exercise training methods for patients with interstitial lung diseases.

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