Effect of Pulmonary Rehabilitation (PR) Programme in patients with Interstitial Lung Disease (ILD)–Indian scenario

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Abstract

Introduction: Interstitial Lung diseases (ILD) are group of disorders wherein due to varied etiologies, interstitium goes into progressive inflammation or fibrosis. Although, the awareness has improved but the therapy is still facing challenges. Pulmonary Rehabilitation (PR) is a worthy modality, which not only supports but also imparts evident benefits in these patients.

Material and Methods: The study is a retrospective observational study conducted over a period of 2 years at Pulmonary Rehabilitation center, a private clinic setup on patients with different restrictive lung diseases like interstitial lung diseases, neuromuscular disorders and post-surgical patients. A total of 100 patients were enrolled, out of which 21 patients were lost to follow up. The study population included 34% males and 66% females with a mean age of 56.3 ± 14.2 years. 24 patients required oxygen support (where SpO₂< 90% at baseline). Outcome measures were assessed in these patients at the time of enrollment into the program (0 week) and at the end of the program (8 weeks). Effect of PR programme was then analyzed with appropriate statistical methods.

Results: Overall, statistically significant benefits were noted in 6 Minute walk distance (6MWD), muscle strength, dyspnea and Quality of life with 8 weeks. The mean 6 MWTD was 297.9 meters pre PR, which improved to 359.7 meters at the completion of 8 weeks post PR. Mean difference was 61.8 meters, which was found to be statistically significant (p value<0.001) Improvement in muscle strength of different upper and lower limb muscle groups were noted. Also, significant improvement in comprehensive score of Chronic Respiratory Diseases Questionnaire (CRDQ) scores was documented. Statistically significant improvement was found in the dyspnea, fatigue and emotional components. However, mastery components did not show statistically significant change.

Conclusion: PR has proven to be a very useful modality in the management of restrictive lung diseases, especially with the known limitations of pharmacological options to treat this disabling chronic lung diseases, even with those with evident type I respiratory failure at the beginning.

Introduction

Interstitial lung disease (ILD) is a group of diffuse parenchymal lung disease characterized by varied etiologies, clinical features and radiological appearance, with a rising morbidity and mortality. It is characterized by acute or chronic inflammation of lung parenchyma leading to fibrosis. Under this broad term of ILD we have major contributions from hypersensitivity pneumonitis, Idiopathic Pulmonary Fibrosis(IPF), connective tissue diseases related ILD, Sarcoidosis and many other miscellaneous forms. Interestingly, heterogeneity lies in all the aspects related to ILD. Exercise limitation has been a common point or rather a hallmark of all the varied forms of ILD. Interplay of multiple contributors has been discovered such as gas exchange limitation due to architectural distortion of capillary bed, circulatory limitation, and reduced diffusion capacity due to thickened alveolar capillary membrane or pulmonary capillary capillary bed destruction. Also, peripheral dysfunction adds to the ongoing embarrassment. Thereby, leading to marked oxy hemoglobin desaturation while exercise. This capillary bed destruction in addition to pulmonary vasoconstriction may lead to pulmonary hypertension. All these mentioned factors play role to limit their exercise capacity pushing them into a so called vicious cycle, where the disabled state leads to exercise limitation and exercise limitation in turn leads to deconditioning. Patients with greater degree of interstitial fibrosis in IPF have more severe diffusion limitation at rest and also show greater oxy hemoglobin desaturation during exercise than those patients with less fibrosing ILD patterns like Sarcoidosis or asbestosis. Typically, patients’ present with progressive exertional breathlessness, dry cough and easy fatigability. These symptoms knowingly or unknowingly withdraw them from their daily activities. Despite a growing understanding of this disease, therapeutic modalities to offer are quite disheartening as yet, in terms of survival benefit. From the era of observation to pharmacological tools in terms of corticosteroids, N acetyl cysteine, azathioprine and then anti-fibrogenic agents, the struggle to herald the fibrosis continues. Where pharmacology is still under evolution, non-pharmacological support in form of Pulmonary Rehabilitation (PR) has shown to benefit these patients. The American Thoracic Society (ATS)/ European Respiratory Society (ERS) statement on PR from 2013 defined pulmonary rehabilitation (PR) as a comprehensive intervention based on a...
Methods

Study design

Our study is a retrospective observational study comprising of 100 patients suffering from restrictive lung diseases, who attended the PR programme over duration of 8 weeks, at an outpatient clinic setup over a period of 2 years. Flow of events are shown in Figure 1.

Setting

Pratibha Prabhakar Pulmonary Rehabilitation center, a private outpatient setup at Goregaon, Mumbai

Methodology

A total of 137 patients with restrictive lung disease were referred for pulmonary rehabilitation to Pratibha Prabhakar Pulmonary Rehabilitation Centre over a period of 2 years. Out of these, 100 patients were enrolled into the program. Patients with restrictive lung disease namely nonspecific interstitial lung disease (NSIP), Idiopathic Pulmonary fibrosis (IPF), unclassified interstitial lung disease (U-ILD) and other restrictive lung conditions (structural and post-surgery cases) were included in the study. The diagnosis of restrictive lung diseases, was made based on a complete pulmonary function test (PFT) and high-resolution computed tomography (HRCT) supported with a detailed history. Where possible and indicated, lung biopsy (transbronchial lung biopsy and VATS guided lung biopsy) was performed. A subset of patients also underwent bronchoscopy to rule out infection, as per clinical indications. As a pre requisite to enrollment, all patients underwent a detailed assessment of clinical history, investigation and comorbidity status assessment (diabetes mellitus, hypertension any orthopedic and psychological conditions) by a pulmonologist and by other fraternity physicians where needed. All baseline routine blood investigations along with their cardiac function parameters with an electrocardiogram (ECG) and 2D ECHO were documented. A written informed consent was obtained. The study population included 34% males and 66% females with a mean age of 56.3 ± 14.2 years. Thereafter, all the patients referred for the PR programme were primed about the program in terms of utility, schedule, components and realistic benefits. Outcome measures namely aerobic capacity (6 MWT), muscle strength and Quality of life (CRDQ) were assessed in these patients when they enrolled into the program (0 week) and at the end of the program (8 weeks).

Aerobic capacity: 6 minute walk test

The aerobic capacity was evaluated using the 6-minute walk test (6MWT) and the distance (6MWT) was documented. The test was performed according to the American Thoracic Society (ATS) guidelines. The heart rate (HR), blood pressure (BP), oxygen saturation (SpO2), respiratory rate (RR) and rate of perceived exertion (RPE) were assessed pre, post and 3 minutes after the test (10). Patients whose basal SpO2 was less than 90%, and who were on who were on long term oxygen therapy; 6MWT was done with supplemental oxygen. 6MWT walked by the patient was calculated, documented and analyzed.

Muscle Strength

The muscle strength was assessed using the submaximal 10 repetitions maximum (10RM) method. The lung foundation of Australia recommends using the 10 RM method instead of the 1RM method in pulmonary patients to assess muscle strength as there may be concerns regarding joints, ligaments and bone density in many of these patients. In addition, it is a safer method as it avoids unnecessary muscle soreness and injury in an already weak muscle. Upper limb muscles namely biceps, triceps, shoulder flexors, shoulder abductors and lower
Pulmonary Rehabilitation is a beneficial modality to aid therapy in patients with interstitial lung disease (ILD). Our study supported the notion that PR could be done on an outpatient setting only. The study population included 24 patients who were given a structured outpatient exercise training program. The program comprehensively offered breathing exercises, exercise training, and patient education. Breathing training comprised of breathing techniques ( pursed-lipped, diaphragmatic breathing, intercostal and segmental breathing), pacing and energy conservation. Exercise training involved aerobic (level walking, treadmill and stationary bicycle) and resistance training (light weights, resistance bands, and dumbbells). Intensity and duration of PR were gradually increased to build tolerance and confidence with the goal of reaching maximum tolerated workload during each exercise period. Supplemental oxygen was given to maintain minimum oxygen saturation of 90%, in patients whom desaturation was observed at rest and during the 6MWT. Regular educational sessions were conducted aiming at promoting coping strategies, management of infections and exacerbations, dyspnea, use of oxygen, return to activities of daily living, and maintaining and improving physical function. In addition, advice on nutrition was provided by dietician. Patients also received psychosocial support.

Statistical analysis

Data was entered in Microsoft Excel and analyzed using Stata Version 13. For linear variables, mean, medians, standard deviation and Inter Quartile Ranges (IQR) were calculated and for categorical variables, proportions were used. Paired t-test was used to compare mean between two groups (pre-and post-means respectively). Distribution of continuous variables across multiple groups, were assessed using the Kruskal Wallis test. *p* value of less than 0.05 was considered to be statistically significant.

Results

A total of 137 patients were referred for pulmonary rehabilitation program over a period of 2 years at our center. Of these, 100 patients got enrolled in the study. Study population included 34(34%) males and 66(66 %) females, with a mean age of 56.3 ± 14.2 years. Most common diagnosis was Idiopathic Lung Fibrosis (IPF) found in 28(28%) followed by other restrictive lung diseases in 25(25%), hypersensitivity pneumonitis in 20(20%), other patterns of restrictive lung disease in 14(14%) and Non-specific interstitial pneumonitis (NSIP) pattern of ILD in 13 (13%). We found that Pulmonary Rehabilitation had beneficial effects on patients, both subjectively and objectively at the end of 8 weeks as depicted in Table no.1. On comparison, patients when performed 6MWT, the mean 6 MWTD was 297.9 meters pre PR, which improved to 359.7 meters at the completion of 8 weeks post PR. Mean difference was 61.8 meters, which was found to be statistically significant (*p value*<0.001) and more than the Minimal clinically important distance (MCID) value in ILD. In subgroup analysis of patients with IPF, mean 6MWD was 276 meters pre PR, which improved to 335 meters at the end of PR. Thus, a significant gain of 59 meters was evident (Figure 2). In our study, 24 patients were given oxygen support (where SpO2< 90% at baseline) and eventually at the end of 8 weeks 6 were lost to follow up.

Exercising capacity of muscles was analyzed by measuring the muscle strength of both upper limb and lower limb muscles by 10RM method. There was statistically significant improvement in different muscle group namely biceps, triceps, shoulder flexors, shoulder adductors, hamstring and quadriceps group, as depicted in Figure 3 when measured at the end of 8 weeks PR program as compared to that at beginning. Similar results were appreciated in patients with IPF also. Importantly, we studied Quality of life in all the patients with the help of chronic respiratory disease questionnaire (CRDQ). The questionnaire comprises of dyspnea, fatigue, emotional aspect and mastery. On comparison of parameters pre an post PR, statistically significant improvement was found in 3 variables of CRDQ namely dyspnea, fatigue and emotional status when assessed individually and also in global rating as shown in Figure 4. However, when mastery was analyzed separately, there was improvement perceived clinically but was not statistically significant. Again, similar results were noted in IPF subset as well.

Interestingly, when patients were analyzed depending upon the total duration of their restrictive lung disease, calculated from the time of enrollment to PR program in years, none of the measured variables i.e. 6MWT, aerobic capacity and quality of life, could show statistically significant difference, pre and post PR program as depicted in Table 2. Around 79% of patient could successfully finish 8 weeks of PR program and 21% patients were lost to follow during the study duration, reasons of which were not analyzed as a part of this study.

Discussion

Our study data supported the handful of studies that have been done on effects of PR in ILD patients till date. Improved functional exercise capacity, symptoms and quality of life were clearly demonstrated following a structured outpatient exercise training programme for 8 weeks, using a standard pulmonary rehabilitation training protocol. As in our study, most of the studies evaluated effects of PR in an outpatient setup only.

Pulmonary Rehabilitation is a science, which has evolved over past 40 years till date. It was established as a beneficial modality to aid therapy
for those struggling with chronic lung diseases. Despite the understanding as to how and why PR would help these patients, the concerns have been the quantum and longevity of benefits. PR was never meant to be the primary therapy to chronic lung disease patients. Instead, the goal has been to help them attain the highest possible level of independence to pursue daily activities. It was devised as an adjunct to ongoing therapies to alleviate symptoms, optimize the functional capacity of patients, and inculcate coping strategies in them.15–17

Majority of research has happened in COPD patients. However, PR has been successfully helpful to patients with other diseases as well such as interstitial diseases, cystic fibrosis, bronchiectasis and thoracic-cage abnormalities.18

A prospective study done by Huppmann and colleagues over 11 years, including 402 individuals with ILD showed that pulmonary rehabilitation definitely has benefits on patients with ILD.19 The most common ILD worldwide is Idiopathic Pulmonary Fibrosis (IPF). In the recent management guidelines published in 2011, PR has got a weak recommendation in IPF as well.20 Point to be understood here is that there has been a moderate quality of evidence for improvement in functional status and patient-oriented outcomes, dilemma still hovers over duration of benefits. These statements do not dilute the favorable impact of PR, but insist on more of research after consolidating the spectrum and extent of benefits of PR in this domain of chronic lung disease.

### 6 minute walk test (6 MWT)

Following 8 weeks of PR programme, we found a significant improvement in 6MWD of 359.7 ± (76.6) m, which was 20.8% of the baseline value (Figure 5). The mean difference in distance covered pre and post PR was 61.8 meters, which was clearly more than minimal clinically important distance (MCID) in not only ILD but also COPD patients across the world. When IPF patients were analyzed separately, with 8 weeks PR programme 59 m of gain was noted in 6MWD was found. However, we lack a clear cut off value of MCID in ILD patients as yet but for COPD patients 54 m is accepted as significant. When results were compared among the different groups of restrictive lung disease, we did not observe any significant difference in improvements in 6MWD before and after PR.8

Across the world when literature on ILD patients was analyzed, our findings matched with almost all the available work in this area. Holland et al in 200821 reported a mean increase in the 6MWD of 35 m in ILD patients and of 25 m in a subgroup analysis of 34 patients with IPF. Nishiyama et al22 observed a PR effect of 46 m in 6MWD. In 2009, Ferreira et al23 measured an average increase of 56 m in their study with 113 ILD patients. Subsequently in 2011, Swigris et al24 documented an improvement of 61 m in 6MWD in their study of 21 IPF patients.

Our results were in concordance with most of them with some variability in the amount of increment in the distance covered, walked post PR as depicted in table 3. 6 MWT has been taken as a surrogate marker of functional exercising capacity of patients with ILD, which uncovers decompensation when patients are made to walk at their own pace. Improvement

### Table 1: Effect of PR program on patients’ parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre PR Mean ± (SD)</th>
<th>Post PR Mean ± (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWTD</td>
<td>297.9 ± (78.9)</td>
<td>359.7 ± (76.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Muscle Strength</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biceps</td>
<td>1.54 (0.71)</td>
<td>2.39 (0.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triceps</td>
<td>0.88 (0.47)</td>
<td>1.90 (0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shoulder Flexors</td>
<td>1.32 (0.71)</td>
<td>2.27 (0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shoulder abductors</td>
<td>1.26 (0.68)</td>
<td>2.23 (0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quadriceps</td>
<td>1.41 (0.74)</td>
<td>2.40 (1.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hamstrings</td>
<td>1.11 (0.56)</td>
<td>2.36 (1.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRDQ Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2.02 (1.19)</td>
<td>4.30 (1.24)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.66 (1.03)</td>
<td>4.81 (0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mastery</td>
<td>4.53 (0.85)</td>
<td>4.47 (0.75)</td>
<td>0.57</td>
</tr>
<tr>
<td>Emotional</td>
<td>4.09 (0.93)</td>
<td>4.93 (0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total CRDQ Score</td>
<td>14.27 (2.56)</td>
<td>18.40 (2.44)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of variables depending upon the duration of diagnosis at the time of initiation of PR program

<table>
<thead>
<tr>
<th>outcome measure</th>
<th>Within 1 year of diagnosis</th>
<th>Between 1-5 yrs of diagnosis</th>
<th>More than 5 years of diagnosis</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>33 (33)</td>
<td>44 (44)</td>
<td>23 (23)</td>
<td>0.68</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>6 (18)</td>
<td>11 (25)</td>
<td>4 (17)</td>
<td></td>
</tr>
<tr>
<td>Outcome measure</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td>Median (IQR)</td>
<td></td>
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</tbody>
</table>

Within 1 year of diagnosis: 6MWD 64 (48, 104), Fatigue 1 (0.5, 1) Shoulder flexors 1 (0.5, 1) Shoulder abductors 1 (0.5, 1)
Between 1-5 yrs of diagnosis: 6MWD 56 (32, 96), Fatigue 1 (0.5, 1) Shoulder flexors 1 (0.5, 1) Shoulder abductors 1 (0.5, 1)
More than 5 years of diagnosis: 6MWD 56 (24, 80), Fatigue 1 (0.5, 1) Shoulder flexors 1 (0.5, 1) Shoulder abductors 1 (0.5, 1)

**Fig. 3:** Improvement in muscle strength pre and post PR

**Fig. 2:** Improvement in 6MWTD pre and post PR
in the distance travelled aids to define effectiveness of an intervention.

**Quality of Life (QOL)**

CRDQ score, which was chosen as a tool to assess the quality of life showed significant improvement post PR of 8 weeks. It comprises of 4 components namely dyspnea, fatigue, emotional status and mastery. Dyspnea when asked for pre and post PR, there was a significant improvement perceived in ongoing dyspnea (p value<0.001). Likewise, extent of fatigue and emotional status when analyzed, post PR showed significant improvement with PR (p value < 0.001) as depicted in Figure 6. However, when mastery was taken individually did not show significant improvement significant with PR at 8 weeks. Holland et al, Nishiyama et al and Vainshelboim et al showed similar findings of statistically significant improvement in dyspnea and overall scores validating enhancement in QOL. CRDQ score was utilized by Holland et al and Perez Bogad et al. Both demonstrated favorable results in CRDQ, although the later couldn’t meet the statistically significant levels.

Where the advancements in medicine still is facing challenges to offer enthusiastic options in pharmacological therapies to this subset of patients, at least PR helps by alleviating the symptoms which is of a paramount importance by preventing them from falling in the vicious cycle of deconditioning and poor exercise tolerance. Benefits in QOL and symptoms cannot be ignored even if they stay short term and may indicate to continue PR as a regular part in patient care, although more research is needed to support the same.

**Muscle strength**

We found a significant improvement in muscle strength post PR programme when assessed at the end of 8 weeks. Biceps, triceps, shoulder flexors, shoulder adductors, quadriceps and hamstrings muscle groups were assessed and compared eventually as per 2013 guidelines. All the p values, were found to be significant (p <0.001), stating that PR programme surely strengthens the peripheral muscle groups in chronic lung disease patients other than COPD as well, which intern would contribute their participation in activities around. Most of the literature supports benefits of muscle strengthening in COPD patients for sure, but the data supporting the same in non-COPD subgroup still continues to be sparse. The official ATS/ERS in 2013 statement did mention the favorable outcomes of PR on muscle strength with resistive / endurance training which should benefit all chronic respiratory disease patients.

Peripheral muscle dysfunction has been a contributor in poor exercise tolerance in ILD too. R kozu et al demonstrated that in patients with IPF, those who had more dyspnea (MMRC grade 4 and grade 5) had greater impairment of quadriceps force and handgrip. This skeletal muscle worsening could have eventually contributed in reduced 6MWD in them. In 2013, ATS/ERS statement on PR clearly stated that peripheral dysfunction contributes to exercise limitation and can be benefitted with PR. This effect can be due to mere physical deconditioning or as side effect of steroids in some. Effects of PR in ILD patients were definitely appreciated although in lesser magnitude and were short-lived up to 6 months duration. To the best of our knowledge, this is the first study in India, analyzing the effect of PR on muscle strength of ILD patients and eventually displaying promising results too.

**Conclusion**

Pulmonary Rehabilitation is a scientifically endorsed modality for patients with chronic lung diseases. We found distinct betterment in bothersome symptoms like fatigue and dyspnea in patients at the end of 8 weeks of PR. We documented improvement in muscle strength, which is a less read parameter. With lesser symptoms and improved muscle strength their participation in activity of daily living improved. Overall, the quality of life showed satisfactory improvement too. It’s no more all about a comfort zone that patient gets, it has rather emerged as a measure that imparts statistically significant enhancements in patient care in terms of both subjective and objective parameters. The assets are better defined and extensively studied in COPD patients and need more research in the remaining chronic lung diseases like ILD with common targets dyspnea, deconditioning and exercise limitation. This study adds asset to the ongoing research on PR with evident lacuna from not only our country but also from majority of the world.

**Limitation of study**

Individual groups were not studied separately for delineating if one had different amount of improvement than rest. ILD is a heterogeneous group of diseases where the progression may vary individually. We could not
perform a subgroup analysis as to establish if there was any difference in the effect of PR. Pulmonary Function test was not included in the study. So effect of PR on lung function wasn’t analyzed, though the effects have been meagre as yet. Reasons for drop out were not included as a part of this study. Follow up of these patients has not been included in this study, to establish the longevity of favorable effects. Also, ongoing pharmacological treatment for various restrictive lung diseases was not documented.

Acknowledgement

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References