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The Efficacy Of Pulmonary Rehabilitation Combined With Threshold Inspiratory Muscle Training And Upper Extremities Exercises In Patients With Interstitial Lung Diseases

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ABSTRACT
Interstitial lung diseases (ILDs) are regarded as crucial chronic lung diseases which are associated with progressive reduction in lung volume, limitations in gas exchange, and dysfunction of skeletal muscle which results in an increased perception of dyspnea, decreased of exercise capacity and impaired health-related quality of life (HRQoL). Pulmonary rehabilitation (PR) in ILD patients remained extremely unidentified with limited studies concerned with this problem. Objective: to evaluate the efficacy of PR program combined with threshold inspiratory muscle training and upper extremities exercises on exercise capacity, pulmonary function test (PFT), dyspnea and HRQoL in ILD patients. Patients and Methods: 60 participants diagnosed with ILD were enrolled between 2016 and 2019. The participants were arranged into two groups equal in number (each 30 participants); study group (A) who received PR accompanied with inspiratory muscle training (IMT) exercises using threshold device and upper extremities exercises in addition to medical treatment, whereas control group (B) received only PR and medical treatment. The program lasted for 8 weeks, three times per week. The outcome criteria included: 6-min walk test (6MWT), PFT, dyspnea (VAS), while HRQoL was measured via the short form 36 (SF-36) questionnaire, moreover, oxygen saturation, all these criteria were evaluated before and after program application (eight weeks apart).Results: There was significant increase in the mean 6MWT distance, PFT, dyspnea and HRQoL after PR compared to baseline criteria within each group, moreover there was significant increase among the study group versus the control group. CONCLUSION: PR accompanied with threshold IMT and upper extremity exercises significantly improved exercise capacity, ventilatory functions, dyspnea and HRQoL in patients with ILD.

Keywords: 6-min Walk Test, Interstitial Lung Diseases, Healthcare-Related Quality of Life, Pulmonary Rehabilitation, Threshold Inspiratory Training Device.

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INTRODUCTION
Interstitial lung diseases (ILD) are not a specific genre of disease but rather an umbrella term of number of lung diseases, which encompasses a variety of diseases with diverse etiology, course, and management. ILD includes impairment in the pulmonary interstitium, the alveolar spaces or airways, blood vessels, and small airways.[1,2] It develops a barrier to gas exchange particularly at the alveolar-capillary interface level and reduces lung dispensability. Therefore, hemoglobin oxygenation decreased with increase work of ventilation resulting in a burden on the cardiorespiratory system. Moreover, skeletal muscle weakness was observed, and it is associated with poor six-minute walking test (6MWT) which is the most applicable method for evaluating exercise capacity among ILD patients[3]. ILDs are the main reason of respiratory mortality and morbidity globally while treatment measures are extremely limited. Moreover, one of these few treatment options is exercise training, which provides positive effects in symptoms as well as exercise tolerance, nevertheless; there is considerable variation in response of the patients due to severity and the etiology of ILD that might affect treatment response.[4]
In this vein, Pulmonary rehabilitation (PR) is regarded as an integrated patient's tailored treatment, employing various strategies such as structured exercise as well as education programs made to enhance the physical as well as psychological disorders of patients who suffer from chronic respiratory diseases.[5] This is a well-established approach that is widely implemented to manage chronic obstructive pulmonary disease (COPD) as it was proven to provide a remarkable amelioration regarding dyspnea and functional capacity. In addition, many studies confirmed the role of PR in different lung diseases such as ILDs.[5,6]

Despite the agreement of the American Thoracic Society/European Respiratory Society (ATS/ERS) on PR supporting its application in managing chronic respiratory diseases, nevertheless its main cause, as data supporting the use of PR, originates largely from the studies of COPD that revealed the positive effect of PR on improving exercise endurance, dyspnea, healthcare-related quality of life (HRQL) and in addition to lower health-care cost. There is emerging data investigating the role of PR in another scheme for chronic lung disease such as ILD.[7]

Therefore, the current study attempted to investigate the efficacy of PR program combined with threshold inspiratory muscle training and upper extremities exercises on exercise capacity, ventilatory functions, dyspnea, and HRQL among ILD patients.

METHODS

Design:

This study was an interventional study; tests were administered before and after the application of the intervention program (8 weeks apart)

Ethical approval:

The ethical committee of the faculty of the Physical Therapy- Cairo University (No: P.T.REC/012/00295), approved the protocol of the current study and each participant signed a prior informed consent form before participating.

Patients:

60 participants diagnosed with ILD based on clinical, radiological, or histo-pathological parameters are willing for PR. Sample size of 30 participants in each group was determined by performing a preliminary power analysis of power 80%. Participants enrolled in this study were from the chest department in Kasr El-Aini, Cairo university hospital in Egypt between September 2016 and December 2019. Inclusion criteria were clinically stable participants i.e. (no changes in drug dose, not hospitalized in the past four weeks, no clinical signs or symptoms of acute exacerbations, not need supplemental oxygen therapy), in addition, physically stable participants i.e. they are capable of walking without aid of an assistive device, having no other serious conditions (cardiac diseases for instance heart failure, cardiac arrhythmia, history of previous lung surgery or a cancer diagnosis), and participants of both genders aged between 30 to 60 years who were referred by a pulmonologist while exclusion criteria included participants with any other chronic lung disease (e.g., COPD, bronchiectasis), cardiac or neuromuscular conditions, history of previous lung resection and any other comorbidities or serious condition that may affect evaluation of results.

The participants of the present study were categorized into two groups; study group (A) who underwent PR accompanied with inspiratory muscle training exercises via employing threshold inspiratory muscle training device and upper extremities exercises in addition to medical treatment, whereas the control group (group B) that received only PR and medical treatment. All participants underwent supervised exercise training three times weekly for 8 weeks, the following measures were obtained: 6MWT to assess exercise capacity, pulmonary function tests (PFT) to assess ventilatory functions, oxygen saturation via pulse oximetry, perceived dyspnea was obtained using the visual analog scale (VAS) (0–10), in addition to the short form 36 (36-SR) questionnaire to measure HRQL. All the tests were performed before and after completion of the program.

Assessments:

- *Exercise capacity Assessment:*
  6-minute walking test (6MWT) was performed based on ATS criteria. Moreover, the distance achieved by participants in 6 minutes was documented in meters by the end of the test. Oxygen saturation, heart rate, as well as degree of dyspnea were evaluated before and after completion of the 6MWT.[8] Oxygen saturation (SpO2) was documented while participants were in sitting position using a Beurer PO 40 Model pulse oximeter (Germany).
- *Pulmonary Function Test (PFT):*
  A specialist performed PFT according to the criteria of ATS.[9] The device using in the PFT was Master Screen PFTpro 2012 Care fusion 234 GmbH, Germany (V-781267-057 version 03.00). Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and the ratio of FEV1 to FVC (FEV1/FVC) values were recorded in the form of percentages of the predicted values.
- *Assessment of Dyspnea:*
  Dyspnea was assessed using Visual analog scale (VAS), It is a horizontal or vertical line, mostly 100-mm long which is commonly employed in the subjective assessment of symptoms including shortness of breath as well as pain, in a particular point in time. It is a 10-point scale based mainly on descriptive terms in order to establish the perception of dyspnea from participants (0 = no dyspnea, 10 = extreme dyspnea).[10] The participants determine which level of dyspnea by highlighting the line separating anchor points in regard to their sensation.
- *Assessment of health-related quality of life*:
  HRQL was assessed using the SF-36, it is composed of 8 multi-component dimensions. These dimensions are physical functioning, physical role; that means role limitations because of physical issues, social functioning, vitality, emotional role which means role limitation because of emotional issues, general health, bodily pain, and finally mental health. Each dimension is rated from 0 to 100, each high result indicating a better health related quality of life.[11] In the current study we applied the Arabic version of the SF-36.[12]

Interventional Procedure:

The participants were instructed about the merits and the benefits of their adherence to PR program besides answering their questions. All participants underwent a PR program, three times/week for eight weeks, and each session lasted 30-45 minutes. It included; controlled breathing exercise (diaphragmatic and pursed lip breathing), breathing exercise consisted of three sets of five times for each exercise with rest between the sets, lung hygiene in form of postural, cough training, and percussion, while endurance training in form of walking exercise (5-20 min/session), the initial endurance training intensity is often set to 70–80% of the maximum exercise capacity, including 6MWT baseline walking speed.[13] Intensity, as well as duration of PR, were increased gradually to build

tolerance as well as confidence to reach the maximum tolerated workload during each exercise period.

Group A received a basic PR program in addition to inspiratory muscle training exercises via threshold IMT device (Ultrabreath, Angle sales company, USA). The participants were instructed 5-10 minutes twice a day and the session included three sets of five loaded inspirations groups, giving one minute rest between sets, and gradually increased according to the rates of perceived inspiratory effort on the modified CR10 Borg Scale (4–6 of 10, moderate level) which was used to determine increment of on training overload.[14] Furthermore, upper limb exercises associated with breathing exercises (trunk extension, pectoral muscles stretch, bilateral shoulder elevation) with 3 sets of 10 times per exercise session.

Statistical analysis:

The IBM SPSS statistics 22 software was performed for statistical analysis. Typically, analysis of data for the current research was done using descriptive statistics and with a 2×2 mixed model Analysis of variance (ANOVA) with two groups (study vs. control) between participants factor and two times for measuring the dependent variables (pretreatment, post treatment) within participant's factor. Post hoc Bonferroni-corrected tests were performed for identifying significant differences between each of the three time of measurements. The P-value was set at 0.05. Before data analysis Shapiro-Wilk test in addition to Levene's test were performed for testing data normality and variances equality, respectively. The differences in demographic characteristics for both groups were subjected to testing using unpaired t-tests as well as Chi-square test.

RESULTS

There was no statistically significant difference among participants, with respect to demographic as well as baseline characteristics between the two groups (Table 1).

Table 1: Comparison of demographic as well as baseline characteristics of participants in both groups

	Group A (n = 30) (mean ± S.D)	Group B (n = 30) (mean ± S.D)	P-value
Age	43.2 ± 9.14	42.5 ± 7.19	0.74
Weight (Kg)	80.63 ± 10.82	79.13 ± 10.9	0.59
Height (m)	1.63 ± 0.07	1.6 ± 0.06	0.23
BMI (kg/m2)	30.52 ± 5.04	30.76 ± 5.16	0.85
6MWT (m)	271.5 ± 32.51	269.33 ± 45.08	0.83
VAS	7.56 ± 0.97	7.46 ± 0.81	0.66
SPO2 (%)	90.13 ± 2.88	90.4 ± 3.43	0.74
FVC	60.34 ± 10.81	59.51 ± 11.77	0.77
FEV1	52.71 ± 12.13	50.60 ± 10.81	0.48
FEV1/FVC (%)	86.85 ± 8.32	85.21 ± 8.41	0.45
PF	28.16 ± 6.62	28.5 ± 6.31	0.84
RF	32.5 ± 8.88	45.16 ± 14.35	0.81
BP	30.6 ± 8.03	31.03 ± 6.85	0.82
GH	31.83 ± 7.24	31.16 ± 6.52	0.7
VT	35.16 ± 5.49	34.5 ± 6.86	0.67
SF	32.23 ± 8.92	33.66 ± 7.7	0.5
RE	36.64 ± 10.19	37.75 ± 11.54	0.69
MH	42.53 ± 10.47	44.13 ± 5.91	0.46

S.D: standard deviation; BMI: body mass index; 6MWT: 6-min walking test; VAS: visual analogue scale; SPO2: oxygen saturation pressure; FVC: forced vital capacity; FEV1: forced expiratory volume in 1s; FEV1/FVC: ratio of FEV1 to FVC; SF-36: the 36-item short-form health survey; PF: Physical functioning; RF: Physical role functioning; BP: Bodily pain; GH: General health perceptions; VT: Vitality; SF: Social role functioning; RE: Emotional role functioning; MH: General mental health.When Comparison the mean values of the results obtained before and after PR application within each group, it was found that there was a statistically significant increase in all variables with percentage of improvement of (25.04, 7.73) in 6 MWT, (3.73, 1.86) in VAS, (7.16, 2.05) in SPO2, (24.52, 5.71) in FVC, (33.27, 8.71) in FEV1, (8.62, 2.76) in FEV1/ FVC, in study group and control group, respectively.

In regard to the SF-36 questionnaire, there was significant increase in all domains as follow; Physical functioning (PF) (86.39%, 41.5%), Physical role functioning (RF) (77.41%, 36.18%), Bodily pain (BP) (82.54%, 46.66%), General health perceptions (GH) (79.57%, 30.48%), Vitality (VT) (70.62%, 18.33%), Social role functioning (SF) (87.18%, 33.12%), Emotional role functioning (RE) (85.01%, 32.45%), General mental health (MH) (45.92%, 16.61%) in the study group as well as the control group, respectively. Upon comparing the outcome measures between both groups at the end of the study a significant increase was observed in all measured variables ($p<0.001$) in favor of the study group (table 2).

Table 2. Comparison of the outcomes of the rehabilitation and control groups

	Group A (n=30)				Group B (n=30)				Post-treatment mean difference between the two groups	P-value
	Pre-treatment (mean ± S.D)	Post-treatment (mean ± S.D)	% change	P-value	Pre-treatment (mean ± S.D)	Post-treatment (mean ± S.D)	% change	P-value		
6MWT	271.5 ± 32.51	339.5± 28.92	25.04	0.0001	269.33 ± 45.08	290.16 ± 46.39	7.73	0.0001	49.3	0.0001
VAS	7.56 ± 0.97	3.83± 1.28	3.73	0.0001	7.46 ± 0.81	5.6 ± 1.0	1.86	0.0001	1.76	0.0001
SPO2	90.13 ± 2.88	96.6± 1.95	7.16	0.0001	90.4 ± 3.43	92.26 ± 3.07	2.05	0.0001	4.33	0.0001
FVC	60.34 ± 10.81	74.42± 9.53	24.52	0.0001	59.51 ± 11.77	62.91 ± 10.78	5.71	0.0001	11.51	0.0001
FEV1	52.71 ± 12.13	70.25± 10.35	33.27	0.0001	50.60 ± 10.81	55.02 ± 10.82	8.71	0.001	15.22	0.0001
FEV1/FVC	86.85± 8.32	94.35± 6.02	8.62	0.0001	85.21 ± 8.41	87.57 ± 9.15	2.76	0.01	6.77	0.001
PF	28.16± 6.62	52.5± 7.16	86.39	0.0001	28.5 ± 6.31	40.33± 8.29	41.5	0.0001	12.16	0.0001
RF	32.5± 8.88	57.66± 11.65	77.41	0.0001	33.16± 12.35	45.16 ± 14.35	36.18	0.0001	12.5	0.0001
BP	30.6 ± 8.03	55.86± 10.01	82.54	0.0001	31.03 ± 6.85	45.51 ± 7.91	46.66	0.0001	10.35	0.0001
GH	31.83 ± 7.24	57.16± 9.79	79.57	0.0001	31.16 ± 6.52	40.66 ± 7.39	30.48	0.0001	16.5	0.0001
VT	35.16 ± 5.49	60.0± 9.46	70.62	0.0001	34.5 ± 6.86	45.5 ± 7.91	18.33	0.0001	14.5	0.0001
SF	32.23 ± 8.92	60.33± 11.68	87.18	0.0001	33.66 ± 7.7	44.81 ± 9.85	33.12	0.0001	15.51	0.0001
RE	36.64 ± 10.19	67.79± 20.5	85.01	0.0001	37.75 ± 11.54	50.01 ± 19.09	32.45	0.0001	17.78	0.001
MH	42.53 ± 10.47	62.06± 9.29	45.92	0.0001	44.13 ± 5.91	51.46 ± 5.22	16.61	0.0001	10.6	0.0001

S.D: standard deviation; BMI: body mass index; 6MWT: 6-min walking test; VAS: visual analogue scale; SPO2: oxygen saturation pressure; FVC: forced vital capacity; FEV1: forced expiratory volume in 1s; FEV1/FVC: ratio of FEV1 to FVC; SF-36: the 36-item short-form health survey; PF: Physical functioning; RF: Physical role functioning; BP: Bodily pain; GH: General health perceptions; VT: Vitality; SF: Social role functioning; RE: Emotional role functioning; MH: General mental health.

DISCUSSION

Herein, this study attempted to investigate the effect of adding threshold IMT device and upper extremities exercise to PR on patients with ILD. The study demonstrated the positive effect of PR among these groups of patients in addition to the routine medical treatment. The current study results showed statistically significant improvement in 6 MWT distance, Dyspnea scale, pulmonary function tests, and HRQoL. Recently, the significance of PR as a comprehensive treatment was proven to improve functional capacity, dyspnea, quality of life in addition to pulmonary functions of a wide range of patients with chronic respiratory diseases including patients with chronic obstructive pulmonary disease (COPD) [15,5] and patients with advanced lung disease who were listed for lung transplantation. [16] Nevertheless, the PR benefits in patients with ILD are not established yet, nonetheless, some studies, including a Cochrane review support the short-term benefits of PR in ILD.[17] It is noteworthy that these studies evaluated PR programs at different durations period and no adverse effects were reported.[13]

6 MWT is a reliable tool for assessing exercise capacity in PR,[18] and considered as an independent mortality indicator in idiopathic pulmonary fibrosis (IPF) as a subtype of ILD.[19] The present research showed significant increase in functional capacity of the participants who underwent PR, with a mean difference of change between both groups estimated at 49.3 meters in favor of the study group. Improved exercise capacity could be attributed to the improved activity level that prevents muscle atrophy as well as improved muscle power and endurance.[20] Moreover, PR may have contributed to alleviating fatigue in patients suffering from chronic respiratory diseases such as ILD. [5] These findings are compatible with the results from randomized control studies, reporting that exercise training can be effective in wide range of ILD with respect to the improvement in the 6MWT distance (>25 m) and QoL.[21]

Graur and colleagues in 2020 conducted a study that attempted to investigate the impact of an IMT program on respiratory muscle strength, functional capacity, physical work capacity, and HRQL of patients, who underwent lung transplantation. Their results showed an improvement in the inspiratory muscle strength associated with improved exercise performance (6MWT distance) and improved HRQL; nonetheless, no insignificant difference exists in values of FEV1, FVC, maximal voluntary ventilation (MVV), in addition to maximal expiratory pressures (MEP).[22]

The ventilatory function also demonstrated a significant improvement in the study group in contrast to the control group, as indicated by the mean difference of FVC, FEV1, and FEV1/FVC ratio. The improvement was a result of the training via IMT device, which improved the function of respiratory muscles, especially inspiratory muscle. Similar improvement was reported in a previous study that found improved FVC values after respiratory muscle training (RMT) and endurance training in patients with ILD.[23]

Dyspnea was significantly improved in the study group in comparison to the control group, with a mean difference change was 1.76, as reflected in the VAS score. The improvement in the dyspnea scale could be attributed to the use of the threshold IMT device which enhanced exercise capacity, ventilatory functions, and respiratory muscle strength[24]. In addition, it was also reported that the use of the threshold IMT device can increase quality of life as well as the ventilatory functions.[24,25] the implementation of unsupported upper extremities exercises (UUEE) in the PR program was also a key in the improvement of dyspnea in the treatment group as UUEE increased muscle endurance as well as the respiratory and thoracic muscle strength. In addition to expanding the rib cage allowing the diaphragm to be in a better position to function more efficiently.[26]

It was proposed that IMT was managed to decrease dyspnea during activities of daily living (ADL), in addition to increasing inspiratory muscle function and quality of life in patients with advanced lung diseases (ALD), moreover these improvements lasted for 3 months.[24]

Owing to the improvement of the previous factors due to the PR program, and the results of the current study showed a significant improvement in HRQL. The data of the current study have shown a significant improvement in all eight SF-36 sub-scores, which is consistent with the finding of Huppmann and his colleagues done at 2013 who investigated the effect of PR in ILD patients on HRQL and their results showed a significant increase in all the eight sub-scores of the SF-36 questionnaires as well as the ventilatory functions; however, there was no significant difference in the scores of dyspnea.[27]

Hoffman and his co-workers in 2019 evaluated the effect of IMT a program of 8-week IMT training conducted at nearly 50 % of maximal inspiratory pressure during ADL on dyspnea, functional capacity, inspiratory muscle function, as well as quality of life in patients with ALD, and their results support the finding of the present study.[24]

Furthermore, the improvement that has been observed among the control group could not have been overlooked, yet this improvement was much less than the improvement which has been observed in the study group, and this finding could be attributed to breathing exercises that helped improve dyspnea, exercise capacity. This finding aligned with previous studies, that investigated the impact of controlled breathing techniques such as diaphragmatic breathing (DB), prolonged exhalation, and pursed lip breathing (PLB) in COPD patients which indicated that the use of these methods has been proven to have clinical effect, for instance, PLB has shown significant efficacy in improving dyspnea, walking distance in the 6MWT as well as gas exchange.[28]

The current study has its limitation, for instance; the small sample size that prevents conducting detailed subtype analyses of these entities. It was difficult to perform a long-term follow-up of PR on the participant and assessing the long-term impact of PR besides participants could not register for long period of time such as 6 or 12 months, therefore, the present study could not detect the long-term effect of PR. Moreover, all the participants enrolled in this study had a baseline mild to moderate lung function impairment, without any case of severe lung derangement, that is why the impact of the PR approach on the sever or deteriorated participants is undetermined, as well as whether more severe functional limitation can significantly affect the improvement after PR. Consequently, more studies are needed to identify the most beneficial subset of patients with ILD who could benefit most from PR.

Despite these limitations, the present study could provide strong data supporting PR in ILD patients. The results of the

current study demonstrated that an 8-week PR program that included different kinds of PR modalities in ILD patients revealed a significant improvement in dyspnea, exercise capacity, HRQoL as well as ventilatory function.

It is firmly advocated that PR is highly recommended as a standard strategy for treating ILD patients,[27] therefore; the present study strongly recommends PR as an effective, feasible as well as safe intervention for ILD patients and may be suggested as part of the standard care program among the targeted group of patients.

Conclusion: PR represents an essential component of the comprehensive care for ILD patients that providing clinically significant improvement in many aspects such as HRQL, exercise capacity as well as improving symptoms. PR has the potential to improve multiple factors at the same time especially cardiovascular performance, muscle strength, and mood disorders.

CONFLICT OF INTEREST

There is no existing conflict of interest.

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