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Effect of Pulmonary Rehabilitation in Patients with Asthma COPD Overlap Syndrome: A Randomized Control Trial

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ABSTRACT

Objectives: We sought to evaluate the effectiveness of six weeks pulmonary rehabilitation (PR) in patients with asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS). ***Methods:*** We enrolled 28 patients with ACOS. Fourteen patients were randomly allocated to the PR group, which comprised of supervised endurance training, supervised resistance training, breathing exercises, self management, and education. The other 14 patients were allocated to the control group, who were asked to continue their usual routine strategies for six weeks. All patients were assessed at baseline and after six weeks using the six minute walk test (6MWT), St George Respiratory Questionnaire (SGRQ), pulmonary function test (PFT), and Bode index (BI). ***Results:*** We saw a significant improvement in 6MWT ($p = 0.001$), SGRQ ($p = 0.007$), and BI ($p < 0.001$) in the PR group after six weeks compared to the control group. There was no significant difference between the groups for PFT ($p = 0.182$) after six weeks. ***Conclusions:*** Use of a short-term PR program in ACOS patients results in favorable changes in functional capacity, health-related quality of life, and BI. However, short-term PR was not sufficient to register changes in pulmonary function in these patients.

Asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome, also known as ACOS, is a unique disease entity that incorporates the co-existence of both asthma and COPD and is often characterized by a persistent airflow limitation. This indicates that ACOS includes two different clinical phenotypes, which are a result of different underlying mechanisms.[1] The global prevalence of ACOS is estimated to range from 25% to 41%,[2] while it ranges between 12.7–55.2% in COPD and 13.3–61% in asthma.[3] A GINA/GOLD document on ACOS recommended that the diagnosis of ACOS should not be based only on spirometric and syndromic features additionally inflammatory biomarkers such as fractional exhaled nitric oxide (FeNO) and blood eosinophils should be used for differentiating ACOS from COPD and asthma.[4,5]

Patients with ACOS tend to have worse clinical outcomes such as frequent exacerbations, rapid decline in lung function, and poor health-related quality of life (HRQoL) compared to those with asthma or COPD alone. All these factors contribute to a higher mortality rate in patients with ACOS.[6–8] A retrospective study conducted by Pleasants et al,[9] reported more dyspnea, higher co-morbidity index, frequent hospitalization, and a higher Bode index (BI) in ACOS patients when compared to asthma and COPD alone. Another study done by Chung et al,[10] reported poor functional exercise capacity in ACOS patients when compared to COPD and asthma groups. Moreover, a recent cross-sectional study also showed lower forced expiratory volume in 1 second (FEV_1) and higher BI in ACOS patients compared to COPD.[6]

Pulmonary rehabilitation (PR) has been well established as a means to alleviate the signs and symptoms of various pulmonary conditions as well as optimize functional capacity, improve exercise tolerance, and HRQoL.[11] The benefit of PR as well

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as its efficacy has been reported previously in both COPD and asthma patients.[12–17] However, the efficacy of a comprehensive PR program in ACOS patients is largely unknown.[18] Considering the worse clinical course in patients with ACOS, there is a need to assess the effectiveness of PR program in this debilitated population. Therefore, our study aimed to evaluate the effects of a six-week comprehensive PR program on functional capacity, HRQoL, pulmonary function, and BI in patients with ACOS. We hypothesized that a six-week program will result in favorable changes in the outcome variables in patients with ACOS.

METHODS

We conducted the study after obtaining ethical clearance from the Institutional Human Ethics Committee of Jamia Millia Islamia, New Delhi, India and from the Metro Ethics Review Board, Metro Hospital Noida, India (16/9/134/JMI/IEC/2017). Patients were diagnosed with ACOS according to syndromic and spirometric features from the GINA/GOLD joint document.[4] The ACOS features which were taken into consideration included: age at onset, pattern and duration of symptoms, pulmonary function, patient's family history, and chest X-ray. Participants in this study fulfilled three or more features of COPD. Furthermore, ACOS patients should have three or more features of asthma as follows: onset before age 20 years, family history of asthma or allergic rhinitis or eczema, normal findings on chest X-ray without severe hyperinflation, common time course in asthmatic patients, variable respiratory symptoms as well as variable expiratory airflow limitation. The common time course included an immediate response to bronchodilator or to inhaled corticosteroids (ICS) over several weeks. Variable respiratory symptoms included shortness of breath that varied over minutes, hours, or days and worsened during the night or early morning. Variable expiratory airflow limitation was defined as improvement in FEV_1 ≥ 200 mL and ≥ 12% from baseline immediately after the use of a bronchodilator or several weeks after the use of ICS. We evaluated these features to confirm ACOS. Furthermore, it was ensured that all patients included in this study were previously investigated for inflammatory markers such as FeNO and eosinophil count. This data was obtained from each patient's medical record. The exclusion criteria for the subjects included contraindications to PR such as a history of myocardial infarction, angina, and congestive heart failure. Patients with any orthopedic or cognitive impairment that would interfere with the regular participation in the rehabilitation program or with any previous history of thoracic surgical intervention were also excluded. Written informed consent was obtained from all participants, and research procedures were conducted in accordance with the Declaration of Helsinki, 1964.

The number of subjects was determined using G. Power 3.15 software (Franz F, Universität Kiel, Kiel, Germany) based on changes in data of St George Respiratory Questionnaire (SGRQ) in a previous study.[19] Fourteen subjects per group were shown to be necessary including 10% dropouts based on the effect size of 0.30, alpha level of 0.05, and power (1-beta) of 0.80.

Twenty-eight ACOS patients were recruited from the pulmonary outpatient department of the Metro Hospital, Noida, India. Patients were familiarized with the study procedures a week prior to the baseline testing. Baseline testing was performed over two days. On day one, following anthropometric assessment, patients were subjected to a pulmonary function test (PFT) and a six minute walk test (6MWT) with an adequate rest period between the two assessments. On day two, patients were asked to fill the SGRQ and the BI was calculated as described by Celli et al.[20] Following baseline testing, patients were randomly allocated using computer-generated block randomization to either the PR group or the control group. The patients in the PR group participated in a six-week comprehensive PR program in addition to the usual care strategies, whereas the control group received usual care strategies alone. All outcomes measures including PFT, 6MWT, SGRQ, and BI were again evaluated after completion of six weeks study period in both the PR and control group.

All patients performed a PFT (JAEGER, Care Fusion) according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[21] The ratio of FEV_1/forced vital capacity (FVC), FVC, and FEV_1 were measured.[22]

The 6MWT was performed in accordance with the ATS/ERS guidelines[23] and parameters such as dyspnea, oxygen saturation (SpO_2), blood pressure,

and pulse rate were measured at the beginning and end of the test. Each patient was asked to walk at his/her own pace to cover maximum distance possible in the allotted time. The distance covered by the patient in six minutes was recorded and reported in meters and percentage. Percentage predicted 6MWD was calculated using the equation proposed by Enright et al.[24]

FOR MEN		
6MWD (% predicted)	=	[7.57 × height (cm)] - (5.02 × age) - [1.76 × weight (kg)] - 309 m

FOR WOMEN		
6MWD (% predicted)	=	[2.11 × height (cm)] - [2.29 × weight (kg)] - (5.78 × age) + 667 m

The SGRQ is a standardized, self-administered questionnaire for measuring HRQoL in airway disease.[25] SGRQ consists of three domains (symptoms, impact, and activity) and a total score. Both English and Hindi version of SGRQ were used as per the language preference of the patient. The SGRQ manual was followed for the administration purposes. Total score was computed by weighted sums of the respective items.[26] The score in SGRQ ranges from 0 (no impairment) to 100 (maximum impairment). A minimally clinically important difference (MCID) of 4 was established for SGRQ by previous research.[27]

The BI is a multidimensional index, which includes four factors that predict mortality: body mass index, the degree of airflow obstruction, functional dyspnea, and exercise capacity as assessed by the 6MWT.[28] A higher score indicates greater risk. The BI ranges from 0 to 10 points, with higher scores indicating a greater risk of death. One unit change in the BI has been suggested as clinically significant.[29]

The patients in PR group attended a structured, comprehensive PR program for six weeks. This PR program was institution based; therefore, the entire exercise protocol was performed under the supervision of a qualified physiotherapist at the hospital. The patients were instructed to report five-times per week at the pulmonary outpatient department. The PR program comprised of stretching of upper and lower extremity muscles, breathing exercises, supervised endurance and resistance training, self-management, and patient education. Patients were administered short-acting bronchodilators (SABDs) through nebulization in both the PR and control groups.

Breathing exercises lasted for 30 minutes in each session and were performed three-to-five times per week for six weeks. Diaphragmatic and pursed-lip breathing were performed as described by previous studies.[30,31] These exercises have been found to reduce respiratory rate and improve tidal volume as well.

Symptom limited cardiopulmonary exercise testing (CPET) was performed as per the guidelines[32] on an electronically braked cycle ergometer (ERGOSELECT 200P/200K; Germany) to calculate the exercise intensity from peak oxygen uptake (VO_{2peak}) achieved during exercise. VO_{2peak} was calculated using a breath-by-breath gas analyzer (COSMED QUARK PFT ergo), which gave data on gases consumed by the patient every 10 seconds. At the beginning of every test, the equipment was calibrated. Incremental exercise protocol was initiated after a period of three minutes rest followed by a three-minute warm-up phase at 0-Watt and was progressed gradually by increasing 5 or 10 Watts according to work rate selection every 60 seconds throughout the exercise phase till the patient got exhausted. The exercise test was followed by three minutes of recovery phase. During the test, patients were encouraged to perform their best and were also instructed to maintain a pedaling frequency of 60 revolutions per minutes (rpm), which was displayed on the digital display of ergometer. VO_{2peak} achieved during the exercise test served as the measure of exercise intensity. Each patient in the intervention group then received an individualized endurance training program at an intensity of 70% to 90% of their respective VO_{2peak} on a motorized treadmill for 20–60 minutes per session, five-times per week for six weeks. A gradual progression of exercise intensity was made from 60–80% of VO_{2peak} over six weeks. During the first two weeks of the program, the intensity was set at 60% of their respective VO_{2peak}. Thereafter, it was increased to at least 70% for the next two weeks and finally, up to 80% during the last two weeks of the training program.[33]

Resistance training of both upper and lower extremity muscles was performed three-times per week at an intensity of 50–70% of one repetition

Table 1: Subject's demographic and clinical characteristics at baseline (n = 28).

Variables	PR group (n = 14)	Control group (n = 14)	*p*-value
Age, years	66.0 ± 8.4	67.0 ± 6.29	0.762
Height, cm	164.0 ± 8.8	159.0 ± 10.3	0.200
Weight, kg	68.0 ± 12.7	58.0 ± 12	0.091
BMI, kg/cm^2	24.0 ± 4.3	23.0 ± 5.1	0.371
Smoking, pack/year	11.0 ± 3.25	11.0 ± 2.9	0.763
FeNO, ppb, median (IQR)	27.0 (22.5)	26.0 (21.5)	0.466
Eo (cells/ uL), median (IQR)	240.0 (129.5–320)	250.0 (138.5–330)	0.098
6 MWD, m	305.4 ± 74.0	313.0 ± 48.1	0.769
6 MWD, %	64.2 ± 13.6	69.4 ± 12.7	0.305
SGRQ			
Symptoms, %	63.1 ± 17.8	65.4 ± 20.6	0.752
Impact, %	59.9 ± 17.2	68.1 ± 19.5	0.253
Activity, %	60.0 ± 16.5	65.0 ± 18.3	0.429
Total, %	62.3 ± 17.9	65.9 ± 19.5	0.612
PFT			
FEV_1, L	1.4 ± 0.4	1.2 ± 0.2	0.236
FEV_1% predicted	65.1 ± 26.7	62.8 ± 15.6	0.671
FVC, L	2.2 ± 0.2	2.0 ± 0.3	0.105
FVC % predicted	71.9 ± 20.9	69.2 ± 14.7	0.720
FEV_1/FVC	47.3 ± 17.9	45.5 ± 17.5	0.784
Bode index	9.3 ± 1.3	8.2 ± 1.9	0.133

Values are expressed as mean±standard deviation unless otherwise stated. Significance level: p < 0.050.
PR: pulmonary rehabilitation; BMI: body mass index; FeNO: fractional exhaled nitric oxide; IQR: interquartile range ; Eo: eosinophil; 6MWD: six minute walk distance; SGRQ: St. George's Respiratory Questionnaire; PFT: pulmonary function test; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

maximum (1-RM). Prior to performing the 1-RM testing, two familiarization sessions were conducted without any load. 1-RM strength was measured to determine the greatest amount of weight that the individual could move in a single repetition. A warm-up of three-to-five minutes followed by 10 repetitions with a light load was performed prior to the test to reduce the effect of learning. The 1-RM test was initiated near the suspected maximum to minimize repetition fatigue. All subjects attained the 1-RM within three-to-five attempts. Subjects were allowed to rest for two to three minutes between attempts.[34] After obtaining the 1-RM, the load at 50–70% of 1-RM was calculated for each exercise. In the lower extremity, quadriceps, hamstring, hip flexors, hip abductors, and hip extensors were exercised. Upper extremity strength training included biceps, triceps, and deltoid muscles. Three sets of 8–10 repetitions of each exercise were performed with two to three minutes rest between sets. Following the rule of gradual progression, exercise intensity was kept at 50% of 1-RM for the first two weeks, 60% of 1-RM for the middle two weeks, and 70% of 1-RM for the last two weeks.[35]

A structured program educating the patients regarding self-management of the symptoms was given in the intervention group (PR group), which comprised of relaxation techniques to control dyspnea, smoking cessation, and nutritional guidelines as per the individualized recommendation of the nutritionist and avoidance of triggers.

The control group continued their activities of daily living along with the medical care in accordance with the standard guidelines by a qualified practitioner.

Data are presented as mean±standard deviation or median (interquartile range). The normality of continuous data was examined using the Shapiro-Wilk test and variables that demonstrated non-normal distribution were log-transformed. Independent *t*-test was used to compare the outcome variables between the PR and the control group at baseline and after six weeks. Standardized mean difference (95% confidence interval) was calculated for the difference observed after six weeks in both

Table 2: Standardized mean difference of outcome variables after six weeks between the groups.

Outcome variables	PR group (n = 14)		Control group (n = 14)		PR group vs. control group Standardized mean difference Random (95% CI), *p*-value
	Baseline	Six weeks	Baseline	Six weeks	
6MWD, m	305.4 ± 74.0	401.9 ± 63.5	313.0 ± 48.1	321.2 ± 43.4	1.44 (0.60,2.29), 0.001*
6MWD, % Pred	64.2 ± 13.6	83.2 ± 11.4	69.4 ± 12.7	71.1 ± 12.6	0.98 (0.19,1.77), 0.014*
SGRQ					
Symptoms, %	63.1 ± 17.8	42.3 ± 12.4	65.4 ± 20.6	61.5 ± 19.8	-1.49 (-2.34,-0.64), 0.005*
Impact, %	59.9 ± 17.2	44.4 ± 13.0	68.1 ± 19.5	63.3 ± 16.9	-1.22 (-2.03,-0.40), 0.003*
Activity, %	60.0 ± 16.5	43.7 ± 12.0	65.0 ± 18.3	63.3 ± 18.3	-1.22 (-2.03,-0.40), 0.003*
Total, %	62.3 ± 17.9	45.5 ± 13.1	65.9 ± 19.5	64.3 ± 20.0	-1.15 (-1.96,-0.34), 0.007*
PFT					
FEV_1, L	1.4 ± 0.4	1.5 ± 0.5	1.2 ± 0.2	1.2 ± 0.2	0.51 (-0.25,1.26), 0.182
%Δ in FEV_1	65.1 ± 26.7	69.3 ± 31	62.8 ± 15.6	64.7 ± 16.4	0.18 (-0.56,0.92), 0.630
FVC, L	2.2 ± 0.2	2.3 ± 0.3	2.0 ± 0.3	2.1 ± 0.3	0.02 (-0.72,0.76), 0.105
% Δ in FVC	71.9 ± 20.9	74.4 ± 20.2	69.2 ± 14.7	70.4 ± 20.2	0.27 (-0.47,1.02), 0.720
FEV_1/FVC	47.3 ± 17.9	49.7 ± 18.1	45.5 ± 17.5	47.0 ± 17.2	0.14 (-0.61,0.88), 0.697
Bode index	9.3 ± 1.3	6.3 ± 1.6	8.2 ± 1.9	8.5 ± 1.9	-1.22 (-2.03,-0.40), < 0.001*

Values are presented as mean±standard deviation.
**Significant difference between groups following six weeks.*
PR: pulmonary rehabilitation; CI: convidence interval; 6MWD: six minute walk distance; SGRQ: St. George's Respiratory Questionnaire; PFT: pulmonary function test; FEV_1: forced expiratory volume in 1 second; %Δ in FEV_1: percentage change in forced expiratory volume in 1 second; FVC: forced vital capacity; %Δ in FVC: percentage change in forced vital capacity.

the groups. Statistical significance was accepted at $p \leq 0.050$. All statistical analyses were performed using SPSS Statistics (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

RESULTS

All 28 participants enrolled in the investigation completed the study. The participant's baseline characteristics are presented in Table 1. There were no significant differences between the PR and the control group for demographic, clinical, and outcome variables at baseline.

After six weeks, there was a significant improvement in 6MWD meters ($p = 0.001$) and percentage predicted ($p = 0.014$) in the PR group compared to the control group. All domains of SGRQ showed significant improvement post-PR [symptom domain ($p = 0.005$), activity ($p = 0.003$), impact ($p = 0.003$), and total ($p = 0.007$)]. BI significantly improved in the PR group ($p < 0.001$). No significant differences were observed in pulmonary function measures FEV_1 (L) ($p = 0.182$), % Δ in FEV_1 ($p = 0.630$), FVC (L) ($p = 0.105$), % Δ in FVC ($p = 0.720$) and FEV_1/FVC ($p = 0.697$) between the groups after six weeks [Table 2].

DISCUSSION

To the best of our knowledge, this is the first randomized control trial to assess the effectiveness of a comprehensive six-week PR program in patients with ACOS. Findings suggest that a six-week PR intervention is an effective treatment adjunct in improving functional capacity, HRQoL, and BI in ACOS patients.

We observed a significant improvement in 6MWD in the PR group by 96 m when compared to the control group. The magnitude of overall increase in distance walked in the PR group exceeded the MCID of 54 m,[36] which is in agreement with the findings of previous investigations[12,13] as they also reported an increase of 66 m and 60 m in COPD and asthma patients, respectively, post-PR. In our study, ACOS patients showed a percentage increase of 29.5% in 6MWD after six weeks of PR. This percentage change observed for the 6MWD in our study is greater in comparison to the change observed by previous studies,[14,15] which were 23% and 25%, respectively. The larger improvement observed in ACOS patients compared to patients with asthma and COPD alone following PR may be due to worse disease status found in ACOS characterized by more dyspnea, a decline in lung function (FEV_1), and lower 6MWD compared to asthma and COPD alone.[37]

Two large systematic reviews and meta-analyses conducted on ACOS have affirmed these findings by demonstrating that patients with ACOS have a greater symptomatic burden.[38,39] We may speculate that patients with worse disease status tend to have a larger capacity to improve compared to patients with more preserved lung function and exercise capacity, in particular, reference to change in 6MWD.

We found a significant improvement in all domains of SGRQ following PR; symptom domain (-20.8 units), impact domain (-15.5 units), activity domain (-16.3 units), and in the total score (-16.8 units). The magnitude of decline observed in all the domains of SGRQ post-PR exceeded the previously reported MCID (decline of 4 points or more).[27] The changes observed in all domains are greater than previously conducted investigations.[40,41] Thus, greater responsiveness of the SGRQ at the end of PR in patients with ACOS compared to patients with asthma and COPD alone may arise as physiological measures related to greater severity of breathlessness, airflow limitation and exercise capacity, which are significant contributors to variance for the total scores of the SGRQ. Furthermore, our study demonstrated that the specific domains of the SGRQ also showed good responsiveness providing the clinician with information regarding changes experienced in relation to symptoms, activity, and impact of the disease. Additionally, at the end of the six-week PR program, the symptom domain showed the highest responsiveness, which might be because of the severity of breathlessness, which has been reported to be higher in patients with ACOS.

We found no improvement in pulmonary function measures in patients with ACOS post-PR. In the context of pulmonary function, there exists contradictory literature. A few investigations conducted previously demonstrated an improvement in pulmonary function,[16,17] while others have reported no changes[42,43] in these parameters post-PR. Our result is in accordance with the previous studies,[42,43] which have demonstrated that the training benefits of rehabilitation are independent of changes in pulmonary function measures. Recent studies[44,45] have also found no significant improvement in PFT following four and eight weeks of PR in COPD patients. The reason for this in our study can be persistent airflow limitation in ACOS group of patients, which might have failed to respond to short-term PR program.[46]

The BI is considered as an important predictor of mortality.[29] Chung et al,[10] reported that ACOS patients have high mortality, which is considered likely due to co-morbidities contributing to health impairment. BI is considered not only an effective prognostic tool for COPD, but its use and validation has also been reported in ACOS.[6] We observed a significant improvement in BI (-3 unit) in the PR group following six weeks, which exceeded the clinically important difference of 1 unit.[47] We found that PR has no significant effect on pulmonary measures, but it significantly improved dyspnea and exercise capacity. These two outcomes, dyspnea and exercise capacity, are components of the BI and thus might have contributed to significant positive change in this index as well.[48,49] In our study, the magnitude of decline in BI was greater than that reported in a previous study,[50] which reported a decline of 2 units post-PR in COPD patients. The greater decline we saw may be due to changes in two components of the BI (i.e., dyspnea and exercise capacity).

The main limitation of our study is the incorporation of short-term PR and, therefore, future research should combat this gap, and it would be interesting to examine the effect of a long-term PR in the unique population of ACOS. Although statistical power was calculated for the study, the sample seemed to be small and, thus, the effect of PR should be assessed on a larger sample in the future. Inclusion of other more relevant outcome variables such as arterial blood gas analysis and inflammatory markers such as Th2 would give a clear picture regarding physiological adaptations to PR in ACOS.

CONCLUSION

A short-term PR program in ACOS patient's results in favorable changes in the functional capacity, HRQoL, and BI. However, short-term PR was not sufficient to register changes in pulmonary function in these patients; therefore, it is important that further long-term randomized control trials should be conducted among this patient group. The findings of our study will pave the way for clinicians in optimizing the effectiveness of PR in patients with ACOS and to gauge the responsiveness of these patients following short-term PR.

Disclosure
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