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Effect of Pulmonary Rehabilitation on Systemic Inflammation Muscle Mass and Functional Status in Interstitial Lung Diseases

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Short Title: Effect of Pulmonary rehab in ILDs

Abstract: ***Background and Objective**: Cytokines play an important role in the pathogenesis of Interstitial lung diseases (ILDs) and several inflammatory mediators have been shown to be increased in ILDs. Pulmonary rehabilitation (PR) programme is a well-established and widely accepted therapeutic tool used in patients with chronic lung diseases like COPD. However, very little is known about the effect of PR over systemic inflammation , muscle mass and exercise capacity in patients of ILDs. **Material and Methods**: Thirty eight patients of ILD were randomised to two groups after enrolment and 4 weeks of standard pharmacotherapy. Group 1 received standard pharmacotherapy and pulmonary rehabilitation for eight weeks while group 2 received standard therapy alone. High sensitivity C-reactive protein (Hs-CRP), mid thigh cross-sectional area CT scan ($MTCSA_{CT}$), pulmonary function test(PFT), six minute walk distance (6MWD), , arterial blood gases (ABG) and lactate levels were measured at the time of enrolment, at 4 weeks and at the end of 12 weeks. **Results**: 18 subjects were randomly allocated to group 1 and 20 subjects to group 2. $MTCSA_{CT}$ showed statistically significant increase at the end of 12 weeks compared to baseline level and 4 weeks in group 1($p_1 = 0.0043$, $p_2 = 0.0089$). Hs-CRP levels showed more reduction in group 1 although not statistically significant($p_1 = 0.1008$, $p_2 = 0.083$). 6mwd showed statistically more improvement in group 1($p_1 < 0.0001$, $p_2 < 0.0001$). Blood lactate ,PFT and blood gases parameters showed no significant changes. **Conclusion**: PR in addition to pharmacotherapy has an important role in improving muscle mass , exercise capacity and functional status and reducing systemic inflammation in the patients of ILDs and should be considered actively in theses group of patients.*

Keywords: Pulmonary rehabilitation, Intertitial lung diseases, CRP, Mid thigh cross sectional area CT scan ($MTCSA_{CT}$), 6MWD

1. Introduction

ILDs are a diverse group of lung diseases that are characterized by chronic inflammation and progressive fibrosis of the pulmonary interstitium. The interstitium is defined as the alveolar walls (including epithelial cells and capillaries), septae, and the perivascular, perilymphatic, and peribroncheolar connective tissues[1]. Data on the prevalence of ILD is scant, and death certificate based mortality data are neither sensitive nor accurate for describing the occurrence of ILDs[2]. The prevalence in New Mexico for all types of ILD was estimated at 80.9 cases per 100,000 population for men and 62.2 cases per 100,000 population for women. The incidence of ILD was estimated at 31.5 per 100,000 persons per year for men and 26.1 per 100,000 persons per year for women. Idiopathic pulmonary fibrosis (IPF) accounted for 46.2% of all ILD diagnoses in men, and 44.2% in women[3]. Comparing the Indian data with epidemiology from the West, IPF remains the most common form of ILD, with familial IPF also being not infrequently encountered. Overall, these data suggest that the spectrum of patients with ILD is very similar to that seen in most Western countries[4].

Cytokines play an important role in the pathogenesis of ILD and several Inflammatory mediators have been shown to be increased in ILDs which include CRP, IL-8, IL-10, TNF-α, IFN□ , IL-2, MMP-9, MMP-7, etc. Pulmonary rehabilitation programme is a well-established and widely accepted therapeutic tool used with standard pharmacotherapy alleviates symptoms, improves the quality of life and, functional capacity in patients with chronic lung diseases like COPD, bronchiectasis and, thus optimize a patient's physical and psychological functioning [5].Exercise training is the cornerstone of pulmonary rehabilitation and is the best available means of improving muscle function in chronic lung disease. However, very little is known about the effect of pulmonary rehabilitation over systemic inflammation , muscle mass and exercise capacity in patients of ILD.

We hypothesized that the pulmonary rehabilitation programme in patients of ILDs would result in decrease in systemic inflammation , increase muscle mass and improve functional status of the patient.

2. Materials Methods

The study was conducted at Vishwanathan Chest Hospital, Vallabhbhai Patel Chest Institute (VPCI), University of

Delhi. Both male and female patients diagnosed as ILD were included in the study from the outpatient department. The diagnosis of ILD was based on clinical history consistent with ILD, pulmonary function test, chest xray and high resolution CT scan (HRCT) and bronchoscopy (broncheoalveolar lavage (BAL) and transbronchial lung biopy (TBLB)).

Inclusion criteria were age more than 18yrs and history, physical examination , PFT consistent with ILD. Exclusion criteria were pregnancy, physiological impairment impeding traing program, presence of systemic disease, acute respiratory infection in the last 4 weeks. The baseline values of the following parameters were measured at the time of inclusion in to the study: Complete pulmonary function test (PFT), high sensitive C-reactive protein (hs CRP) (mg/L), Mid thigh cross sectional area CT ($MTCSA_{CT}$) (mm^2), Six minute walk test (6MWT) (m). All the patients received standard pharmacotherapy as per the BTS guidelines for 4 weeks.[6] The values of all the above parameters were measured again after 4 weeks and the patients were then randomized in to one of the two groups:

Group 1 : Patients received standard therapy with pulmonary rehabilitation for 8 weeks
Group 2 : Patients received standard therapy alone.
At the end of 12 weeks all the study parameters were measured again.

Exit from the Study
1) Patients request
2) Non compliance with study protocol
3) Skipped more than 1 week of training program.
4) Any acute exacerbation requiring hospitalization and use of antibiotics and/or increase in dose of oral steroids.

Pulmonary Function Tests: Spirometry was performed on a computerized apparatus- Benchmark (P. K. Morgan and Co. Ltd. Chatham, Kent England). Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC%, residual volume (RV), Total lung capacity (TLC), Diffusion capacity of lungs for carbon monoxide (DLCO) were obtained as per the recommendations of the American Thoracic Society [7].

Inflammatory marker: Values of high sensitivity C-reactive protein (hs-CRP) were found using the human C-Reactive Protein/CRP Quantikine ELISA Kit (catalogue no. DCRP000), from R&D systems, Inc. USA.

Midthigh muscle cross-sectional area ($MTCSA_{CT}$): A computed tomography of the right and left thigh, halfway between the pubic symphysis and the inferior condyle of the femur was performed using a third generation scanner. Each image was 10-mm thick and was taken at 120 KV and 200 mA with a scanning time of 1 second while the subject was lying in the supine position. The thigh muscle cross-sectional area (CSA) was obtained by measuring the surface area of the tissue with a density of 40 to 100 hounsfield units (HU). The $MTCSA_{CT}$ was calculated by taking average for right and left thighs cross sectional area.

Six minute walk test (6mwt): 6MWT was performed on a flat, straight, enclosed corridor with a hard surface as per the ATS guidelines [8].

Pulmonary rehabilitation program: The pulmonary rehabilitation program comprised minimum of 90 minutes of supervised exercise training for lower and upper limbs, performed over separate sessions each day, three days a week, for 8 weeks. Lower limbs training included leg-ergometry and treadmill walking. Training of the upper limbs included arm-ergometry and free weights. Simultaneous upper and lower limb training was performed on Semi-Recumbent Whole Body Exerciser. Exercise intensity during each session was incremental and graded according to symptom tolerance and was of 20 minutes duration. Patients also attended educational sessions on topics such as breathing exercises, energy conservation, lung health, medications and stress management [5].

3. Statistical Analysis

Statistical analysis was done using Graph pad 5.03 version. The data were presented as mean ± standard error (SE). The difference in the mean baseline values of various measurements within the group and between the groups was made using student's t-test. A p value of <0.05 was considered significant.

4. Results

In a period of one year, thirty eight subjects were recruited, out of which 18 subjects were randomly allocated to group 1 and 20 subjects to group 2. The demographic and clinical characterstics of the two groups are given in the table 1.

There was no significant difference in age, sex, BMI, duration of disease, pack years between two groups. Mean values of pulmonary function test were comparable between two groups without any significant difference. Mean hsCRP value was higher in both the groups. Mean values of $MTCSA_{CT}$ and 6MWT were comparable without any statistical significant difference in both the groups. Mean values of Pao_2, $Paco_2$, So_2, lactate levels were comparable in both the groups. Decrease in hsCRP mean value at the end of 12 weeks was found as compared to baseline level in both the groups but the effect is more profound in rehabilitation group (although not statistically significant) (Table 2& 3, Fig 1). $MTCSA_{CT}$ showed statistically significant increase at the end of 12 weeks compared to baseline level and 4 weeks in group 1(table2 &3, fig 2). At the end of 12 weeks, six minute walk test showed statistically significant improvement from baseline in both the groups and from 4 weeks only in group 1(table 2&3, fig 3). Arterial blood gas parameters, blood lactate levels and pulmonary function tests did not show significant change at the end of 16 weeks in both the groups. Comparison of various parameters of group 1 and group 2 are tabulated in table 2 and table 3 respectively.

5. Discussion

In this study, serum levels of markers of systemic inflammation along with blood lactate, pH, paCO2, paO2, Sao2 , pulmonary function tests, $MTCSA_{CT}$ and 6MWT were analysed in thirty eight interstitial lung diseases patients. We also studied the effects of pulmonary rehabilitation on the above mentioned parameters compared to the patients receiving standard pharmacotherapy only. Both the groups were comparable by demographic characterstics and clinical parameters. There was no significant change in pulmoinary function test (FEV_1%, FVC%, FVC, FEV_1, FEV_1/FVC , RV, RV/TLC, DLCO, DL / Va) and arterial blood gas(Sao_2, Pao_2, $Paco_2$, blood lactate levels and pH) from 4 weeks to end of 12 weeks in both group 1 and group 2 .

Alveolar and interstitial inflammation in ILD is an important pathway in the development of lung injury and subsequent fibrosis. Neutrophils and neutrophil products have been identified in increased amounts in the airspace of patients with ILD and in animal models of lung fibrosis[9].CRP reflects total systemic burden of inflammation of individuals and is used as a predictor of hospitalization and mortality in patients with chronic respiratory failure. It is higher in patients in patients with poor FEV_1value and in those who smoke. CRP level predicts cardiovascular mortality. Drent and coworkers demonstarted that a moderate increase in serum CRP is implicated in Sarcoidosis [10]. Richards et al showed that high serum levels of CRP were found in myositis associated ILDs [11]. In the present study, CRP levels were higher in both the groups of ILD patients supporting the results of previous studies. Mattusch and colleagues investigated the influence of exercise training on CRP level in healthy subjects. The baseline CRP level in 10 out of 12 runners was significantly reduced after training[12]. This study therefore supports the view that intensive regular exercise has a systemic anti-inflammatory effect in healthy subjects and the research has potential implications for patients with ILDs. HERITAGE Family Study of exercise in healthy sedentary individuals also suggested that beneficial reductions in CRP levels after training are greatest in those with baseline levels higher than 3 mg/L [13]. In our study group mean CRP level in group 1 at baseline was 6.186 ± 1.075 mg/l. In addition, we found CRP levels were decreased, although not significantly, in both the groups compared to baseline level. The decrease in mean CRP level in group 1 at the end of 12 week was more than group 2 although the difference was not statistically significant (p = 0.08). Apart from exercise, the medications that can decrease CRP level include inhaled and systemic corticosteroids. The patients in our study receiving pharmacotherapy in the form of corticosteroids and other immunosuppressive drugs were given the same dose of drugs throughout the study period. The decrease in mean value in both the groups might be due to the absence of infection and exacerbation during the entire study period which are known to increase the CRP levels. Although not statistically significant but the more decrease in CRP level in group 1 indicates that pulmonary rehabilitation may have additive effect on the decrease in CRP level in addition to phrmacotherapy. This will provide a promising aspect for further research and highlights the importance of pulmonary rehabilitation in the management of ILD.

Body weight loss is seen in patients with ILD. Although body weight is a useful prognosis marker in ILD, it is not sensitive to changes in body composition as it can be increased or normal despite the presence of muscle wasting .Marquis et al used $MTCSA_{CT}$ in their study and found that $MTCSA_{CT}$ is a better predictor of mortality than body mass index and $MTCSA_{CT}$ has a strong impact on mortality in COPD patients with an FEV_1 < 50% predicted[14]. Fiatarone et al found a significant increase in mid-thigh muscle area with marked increases in both quadriceps (9%) and hamstring and adductor areas (8.4%) in response to 8 wk of resistance training, without changes in subcutaneous or intramuscular adipose tissue[15]. In our study, the mean value of MTCSA in group 1 at the end of 12 weeks was increased to 9696 ± 463.5 mm2. The increase in mean value from 4 weeks and baseline was clinically significant (p= 0.0089 (4weeks) , p= 0.0043 (baseline)). The mean value of MTCSA in group 2 at the end of 12 weeks was increased to 9599 ± 446.2 mm2. The increase in mean value from 4 weeks and baseline was not clinically significant (p= 0.6208, p= 0.1793).

Thus ILD patients on rehabilitation along with medications show an increase in $MTCSA_{CT}$. To the best of our knowledge, no follow up study has been done to see the change in $MTCSA_{CT}$ value during the course of disease in patients with medications, as well as on the effect of pulmonary rehabilitation on $MTCSA_{CT}$ in ILD patients. Muscle wasting should be considered as a serious complication in ILD like other chronic illnesses such as COPD with important implications for survival. Gain in muscle mass and strength seems to be associated with better exercise tolerance and probably survival of ILD patients. Thus, improving peripheral muscle function and muscle mass would be a reasonable therapeutic target in these groups.

6MWT is used to assess the functional capacity in ILD and other chronic respiratory diseases patients. This minimum clinically important distance (MCID) of 54m is based on the cross-sectional study of Redelmeir on 112 COPD patients attending a residential pulmonary rehabilitation program[16]. Lederer et al showed that the lower 6MWD is strongly and independently associated with an increased mortality rate for wait-listed patients classified as having IPF for lung transplantation and 6MWD was a better predictor of death at 6 month than was FVC % predicted[17].

Holland AE showed that small differences in six-minute walk distance (6MWD), in the range 29–34 m, may be clinically significant for people with diffuse parenchymal lung disease[18]. In our study, the mean value of 6MWT in group 1 was 403.2 ± 14.74 m. The mean value of 6MWT in group 2 was 444.2 ± 17.53 m (p= 0.0860). The mean value of 6MWT in group 1 at the end of 12 weeks was increased to 457.9 ± 14.6 m compared to baseline (p< 0.0001) while in the group 2 it increased to 460.7 ± 18.6 m at the end of 12 weeks compared to baseline (p= 0.0375). The difference in 6MWD in group 1 was 54.7m while in group 2 it was 16.7m at the end of 12 weeks. Thus in patients who received

rehabilitation along with standard treatment, the mean increase from baseline to end of 12 weeks was above the threshold of clinical significance (54m) whereas in group 2 who received standard treatment alone the mean increase on both the occasion was below the threshold of clinical significance. The impairment of exercise capacity is a central issue in patients with ILD patients. In clinical practice, the 6-minute walk test (6MWT) and the incremental shuttle walking test are commonly used to assess changes in functional exercise capacity following pulmonary rehabilitation with the primary outcome reported being the distance walked during the test. The 6MWT is also be used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality in ILD patients [17]. Our study has few limitations. Sample size of the study is small and thus a randomized control study with large sample size is needed to generalize the results. Moreover, the observation period in this study was restricted to the active PR period i.e 12 weeks. Long-term follow-up data are not available; consequently, the long-term effect of PR remains unknown. Thus, whether the improvement conferred by PR is sustained or not is not known. We conclude that pulmonary rehabilitation program with exercise training, upper-limb, trunk, lower limb, respiratory muscle training is highly effective in improving the exercise capacity of patients of ILD compared to patients who receive standard medications only.

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Table 1: Demographic and Clinical Characteristics of Group 1 and 2

Parameters	*Group 1*	*Group 2*	*p Value*
	MEAN ± S.E	MEAN ± S.E	
Age (Years)	52.17 ± 2.416	47.55 ± 2.127	p = 0.1585
BMI (kg/m^2)	26.31 ± 1.066	24.98 ± 0.9271	p = 0.3506
Male: Female	7:11	9:11	
Occupation (indoor:outdoor)	5:1	3:1	
Pack Years	5.000 ± 2.425	3.250 ± 1.508	p = 0.5351
Disease duration (yrs)	4.250 ± 0.4753	3.763 ± 0.3505	p = 0.4083
O_2 Saturation (%)	95.67 ± 1.68	94.75 ± 2.32	P= 0.22
Respiratory Rate	23.83 ± 0.3898	23.20 ± 0.5601	p = 0.3696
Hb (g/dl)	12.94 ± 0.3511	12.69 ± 0.3638	p = 0.6195

Table 2: Comparison of Various Parameters in Group 1 (N= 18):

PARAMETERS	*AT BASELINE*	*AT 4 WEEKS*	*AT 12 WEEKS*	*P value*
	MEAN ± S.E	*MEAN ± S.E.*	*MEAN ± S.E*	
hsCRP (mg/L)	6.186 ± 1.075	5.794 ± 0.8470	5.286 ± 0.7400	p_1= 0.1008, $p_{2=}$ 0.0838
$MTCSA_{CT}$ (mm^2)	9255 ± 454.2	9336 ± 464.6	9696 ± 463.5	p_1= 0.0043 p_2= 0.0089
6MWD (m)	403.2 ± 14.74	411.6 ± 15.27	457.9 ± 14.06	p_1< 0.0001 p_2< 0.0001
Lactate (mmol/L)	1.294 ± 0.171	1.156 ± 0.1181	1.011 ± 0.1174	p_1= 0.0920 p_2= 0.2067
Pao_2 (mmHg)	63.18 ± 2.304	63.72 ± 2.148	64.17 ± 1.905	p_1= 0.2235 p_2= 0.4395
$Paco_2$ (mmHg)	40.62 ± 1.146	39.32 ± 1.183	39.27 ± 0.8807	p_1= 0.2502 p_2= 0.9631
Sao_2 (%)	90.89 ± 1.527	91.84 ± 1.241	92.56 ± 1.155	p_1= 0.0896 p_2= 0.1277
FEV_1 (L)	1.507 ± 0.108	1.553 ± 0.1189	1.577 ± 0.1204	p_1= 0.2934 p_2= 0.3905
FEV_1% PRED	65.67 ± 4.487	66.22 ± 4.732	67.28 ± 4.584	p_1= 0.7261 p_2= 0.4439
FVC (L)	1.792 ± 0.127	1.859 ± 0.1414	1.894 ± 0.1422	p_1= 0.2199 p_2= 0.3905
FVC % PRED	64.17 ± 4.224	65.61 ± 4.152	66.67 ± 4.483	p_1= 0.3146 p_2= 0.4811
RV(L)	0.99 ± 0.07455	1.066 ± 0.09290	1.154 ± 0.1056	p_1= 0.3671 p_2= 0.1726
TLC(L)	2.717 ± 0.1394	2.889 ± 0.1581	3.125 ± 0.1951	p_1= 0.1136 p_2= 0.0600
RV/TLC(%)	36.94 ± 2.376	37.72 ± 2.459	39.56 ± 2.635	p_1= 0.6393 p_2= 0.0542
DLCO(ml/min/mmHg)	8.753 ± 0.9466	9.246 ± 1.025	9.819 ± 1.004	p_1= 0.6393 p_2= 0.1726
pH	7.417± 0.01057	7.403 ± 0.005900	7.40 ± 0.005562	p_1= 0.2525 p_2= 0.3516

P_1= P value for baseline and 12 week observations, P_2 = p value for 4thweek and 12^{th} week observations

Table 3: Comparision of Various Parameters in Group 2 (N= 20):

PARAMETERS	*AT BASELINE*	*AT 4 WEEKS*	*AT 12 WEEKS*	*P value*
	MEAN ± S.E	MEAN ± S.E	MEAN ± S.E	
hsCRP (mg/L)	4.328 ± 1.072	4.057 ± 0.7987	3.744 ± 0.6536	p_1= 0.3311 p_2= 0.3669
$MTCSA_{CT}$ (mm^2)	8893 ± 593.9	9493 ± 472.5	9599 ± 446.2	p_1= 0.1793 p_2= 0.6208
6MWD (m)	444.2 ± 17.53	452.3 ± 16.24	460.7 ± 16.18	p_1= 0.0379 p_2= 0.2743
Lactate (mmol/L)	1.095 ± 0.1042	1.055 ± 0.08750	0.9440 ± 0.09273	p_1= 0.2096 p_2= 0.2908
Pao_2 (mmHg)	70.21 ± 2.853	70.20 ± 2.607	66.60 ± 3.903	p_1= 0.9835 p_2= 0.3307
$Paco_2$ (mmHg)	39.25 ± 1.555	40.56 ± 1.225	40.58 ± 1.456	p_1= 0.1377 p_2= 0.9842
Sao_2 (%)	94.35 ± 1.047	93.90 ± 0.9372	94.10 ± 0.8672	p_1= 0.2596 p_2= 0.5688
FEV_1 (L)	1.762 ± 0.2249	1.835 ± 0.2604	1.826 ± 0.2012	p_1= 0.1882 p_2= 0.7676
FEV_1% PRED	62.90 ±5.351	64.20 ± 5.336	63.60 ± 5.387	p_1= 0.2759 p_2= 0.5669
FVC (L)	2.279 ± 0.2447	2.307 ± 0.2403	2.326 ± 0.2277	p_1= 0.4137 p_2= 0.7676
FVC % PRED	66.25 ± 4.831	67.60 ± 4.751	68.30 ± 4.733	p_1= 0.1841 p_2= 0.6558
RV(L)	0.9755 ± 0.07930	1.067 ± 0.09932	1.200 ± 0.1353	p_1=0.2851 p_2=0.1667
TLC(L)	3.242 ± 0.2696	3.245 ± 0.2759	3.470 ± 0.3108	p_1= 0.9331 p_2= 0.1060
RV/TLC(%)	31.70 ± 2.339	32.30 ± 2.249	33.55 ± 2.029	p_1= 0.7390

				p_2=0.3961
DLCO(ml/min/mmHg)	11.28 ±1.179	11.26 ± 1.154	11.52 ± 1.112	p_1= 0.7390 p_2=0.1667
pH	7.406 ± 0.006728	7.399 ± 0.004588	7.412 ± 0.006923	p_1= 0.1462 p_2= 0.0905
P_1= P value for baseline and 12 week observations, P_2 = p value for 4thweek and 12th week observations				

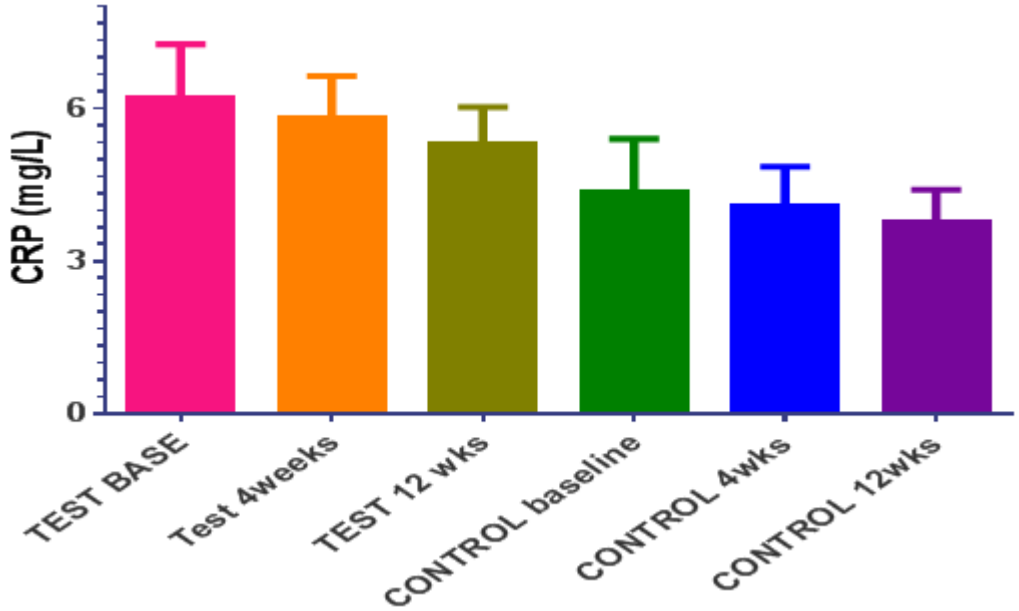

Figure 1: Trends of hS-CRP (mg/L) in group 1 and 2 at baseline, 4th week and after 12 week of study.

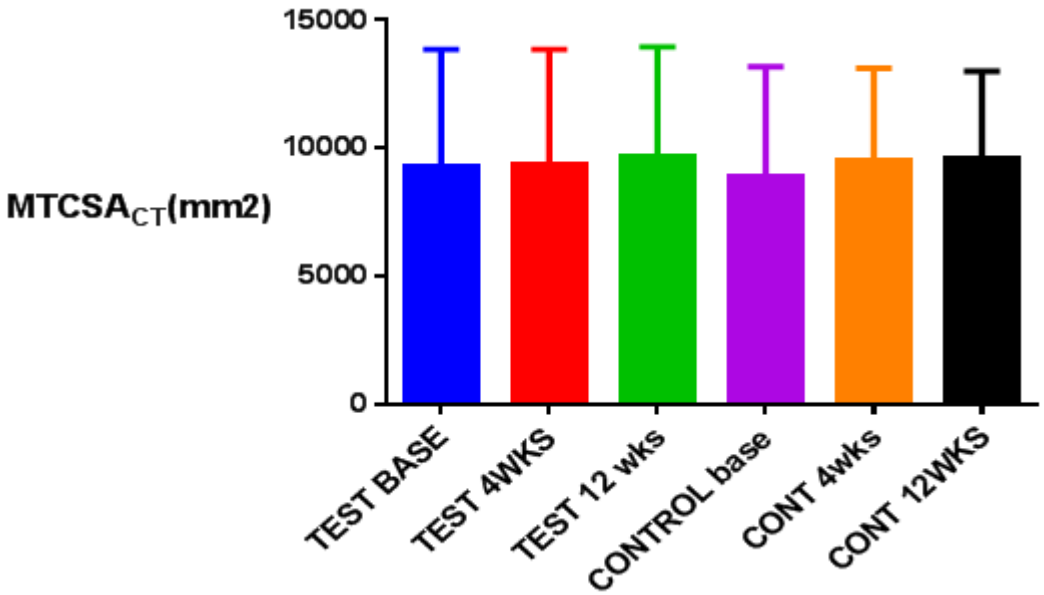

Figure 2: Trends of $MTCSA_{CT}$ in groups 1 and 2 at baseline, 4th week and at the end of 12 weeks.

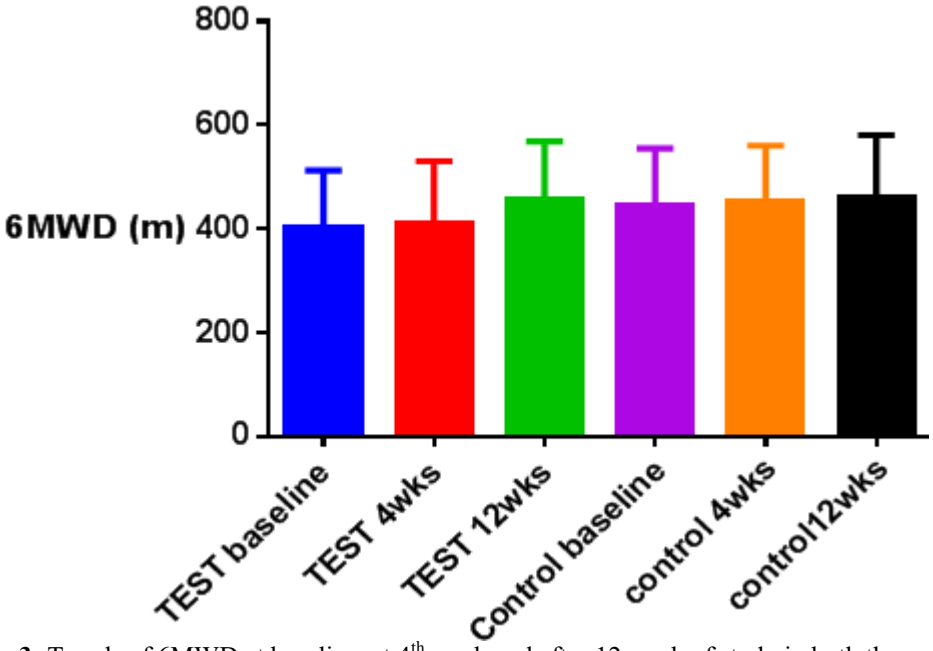

Figure 3: Trends of 6MWD at baseline, at 4th week and after 12 week of study in both the groups.