ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Programmed Exercise in Conjunction with Sildenafil Therapy is Beneficial for patients with Pulmonary Hypertension Secondary to Idiopathic Pulmonary Fibrosis

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Manuscript Info

Manuscript History:

Received: 15 September 2014
Final Accepted: 16 October 2014
Published Online: November 2014

Key words

Exercise, Sildenafil, Pulmonary hypertension, Idiopathic pulmonary fibrosis

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Abstract

Objectives: To evaluate effect of exercise and respiratory training alone or in conjunction with sildenafil on exercise capacity and quality of life (QOL) of patients had pulmonary arterial hypertension (PAH) secondary to idiopathic pulmonary fibrosis (IPF).

Materials & Methods: Patients were categorized into 3 groups (n=12): Group S received sildenafil 25 mg trice/day; Group E underwent exercise intervention and Group ES received both modalities. Exercise consisted of inpatient pulmonary rehabilitation for 30 min/day for 3 weeks (wk) and continued at home for additional 12 wk. Physiologic assessment included determination of FVC, FEV1 and FEV1/FVC using spirometry and arterial blood gases analysis. Outcome was defined as changes from baseline to week 15 in 6-minute walking distance (6MWD), dyspnea scoring by Medical Research Council (MRC), time till exercise intolerance and QOL scoring.

Results: All patients showed improvement of 6MWD, time till exercise intolerance and FVC and FEV_1 and ratio FEV_1/FVC. Frequency of patients had MRC4 was significantly lower, while MRC2 was significantly higher and post-6MWT Borg exertion score showed progressive decrease in all patients. Improvements were more pronounced in groups ES and E compared to group S with significant difference in favor of group ES. Patients of groups E and ES showed significant improvement of ability to ambulate, while the improvement was non-significant in group S compared to baseline scoring. Emotional behavior and recreation were significantly improved only in group ES.

Conclusion: Combined exercise training and sildenafil therapy improved exercise tolerance of patients with PAH secondary to IPF with improved QOL.

Introduction

The pressure gradient in the pulmonary system is about 7 mmHg, pulmonary capillary pressure is about 10 mmHg, whereas the oncotic pressure is 25 mmHg, so that an inward directed pressure gradient of about 15 mmHg keeps the alveoli free of all but a thin film of fluid. When the pulmonary capillary pressure is more than 25 mmHg—as it may be, for example, in "backward failure" of the left ventricle—pulmonary congestion and edema result. Pulmonary blood flow is affected by both active and passive factors. There is extensive autonomic innervation of the pulmonary vessels, and stimulation of the cervical sympathetic ganglia reduces pulmonary blood flow by as much as 30%. The vessels also respond to circulating humoral agents. Passive factors such as cardiac output and gravitational forces

also have significant effects on pulmonary blood flow **(Rouatbi et al; 2006 ,Agoston et al; 2006, Bartel et al; 2008).**
Local adjustments of perfusion to ventilation are determined by local effects of the lack of O_2. When a bronchus or a bronchiole is obstructed, hypoxia develops in the under-ventilated alveoli beyond the obstruction. Oxygen deficiency acts directly on vascular smooth muscle in the area to produce vasoconstriction, shunting blood away from the hypoxic area. On the other side, accumulation of CO_2 leads to a drop in pH in the area, and a decline in pH also produces vasoconstriction in the lungs. Conversely, reduction of the blood flow to a portion of the lung lowers the alveolar P_{CO2} in that area, and this leads to constriction of the bronchi supplying it, shifting ventilation away from the poorly perfused area. Systemic hypoxia also causes the pulmonary arterioles to constrict, with a resultant increase in pulmonary arterial pressure (PAP) **(Dorrington et al; 2010, Crof et al; 2013)**

With exercise, cardiac output increases and PAP rises proportionately with little or no vasodilatation. More red cells move through the lungs without any reduction in the O_2 saturation of the hemoglobin in them, and consequently, the total amount of O_2 delivered to the systemic circulation is increased. Capillaries dilate, and previously under-perfused capillaries are "recruited" to carry blood. The net effect is a marked increase in pulmonary blood flow with few, if any, alterations in autonomic outflow to the pulmonary vessels **(Beck et al; 2012).**

Sildenafil is a selective inhibitor of type 5 phosphodiesterase (PDE5), the predominant PDE isoform responsible for hydrolysis of intracellular cyclic guanosine monophosphate (cGMP) in the pulmonary vasculature. Inhibition of PDE5 enhances the vasodilatory effects of nitric oxide by preventing the degradation of cGMP, which promotes relaxation of vascular smooth muscle and increases blood flow. In animal models and human trials, sildenafil has been found to produce a relatively selective reduction in pulmonary artery pressure without adverse systemic hemodynamic effects. Inhibition of PDE5 by sildenafil may also enhance the platelet antiaggregatory activity of nitric oxide and inhibit thrombus formation **(Ichinose et al; 2001, Shekerdemian et al; 2002)**
Idiopathic pulmonary fibrosis (IPF) is a progressive fibro-proliferative lung disorder of unknown cause characterized by relentlessly progressive restrictive-ventilatory limitation, hypoxia, dyspnea, and cough. IPF is refractory to current therapy and is commonly complicated by the development of pulmonary hypertension (PH) and other serious associated co-morbid illnesses, including chronic obstructive pulmonary disease, gastroesophageal reflux disease, obstructive sleep apnea, obesity, lung cancer, and depression that further contribute to the substantial rise in the use of IPF-related healthcare resources. At present, lung transplantation remains the sole viable treatment for the few who qualify **(Corte et al; 2014, Lee et al; 2014)**

The current prospective study aimed to evaluate the effect of aerobic exercise and respiratory training on exercise capacity and quality of life (QOL) of patients had pulmonary arterial hypertension (PAH) secondary to IPF. Also, the study tried to evaluate the beneficial effect of programmed exercise in conjunction with drug therapy using sildenafil on these parameters.

Materials & Methods

The current study was conducted at Physiology Department in conjunction with Chest Department, Faculty of Medicine, Benha University since Feb. 2012 till June 2014 to allow for a training period of 15 weeks (wk) for the last studied case. After approval of the study protocol by the Local Ethical Committee, files of patients admitted to or on regular follow-up at Chest Department, Benha University Hospital were revised and 36 patients with PAH secondary to IPF were selected to be recruited in the study after singing written fully informed consent and their pre-interventional data were collected. Diagnosis of IPF was established according to the international consensus statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) **(American Thoracic Society; 2000).** PAH was diagnosed by a resting mean pulmonary arterial pressure >25 mmHg as measured by echocardiography.

Inclusion criteria

Enrolled patients must be stable and compensated with medical therapy as corticosteroids, ACE inhibitors, anticoagulants, diuretics and supplemental oxygen for at least 2 months before entering the study. Patients must be sedentary, and had no pulmonary rehabilitation or maintained on sildenafil therapy for 6 months prior to enrollment. Selected patients must be of World Health Organization functional class (WHO-FC) II–IV **(Barst et al; 2004)**.

Exclusion criteria

Patients with WHO-FC I and could walk >400 m during a 6-minute walking test (6MWT), or classified as functional class IV and could not walk >50 m during a 6MWT were not enrolled in the study. Additional exclusion criteria included FEV_1 /FVC ratio <60%; history of ischemic heart disease; ejection fraction <40%; significant hepatic, renal; severe psychiatric disease; use of medications that may limit exercise capacity or ability to adapt to exercise training; tobacco use; or pregnancy.

Grouping

Patients were randomly, using sealed envelopes, categorized into 3 study groups: Group S included 12 patients received sildenafil 25 mg three times daily and not subjected to exercise program; Group E included 12 patients assigned to undergo exercise intervention and Group ES included 12 patients received sildenafil 25 mg trice daily and included in the exercise interventional program.

Methods

1. Dyspnea severity index (DI) was assessed using a 5-point scale of the Medical Research Council (MRC) with grade 0= No dyspnea; grade 1: dyspnea after two flights of stairs; grade 2: dyspnea after one flight of stairs; grade 3: breathlessness on minimal exertion; and grade 4: breathlessness at rest **(Mahler & Wells ;1988)**.
2. 6-minute walking distance (6MWD) test was carried out under standardized conditions **(Guyatt et al; 1985)**. Patients must wear comfortable clothing and appropriate shoes, use their walking aids, if any, during the test and have a light breakfast and their usual treatment. Pulse oximetry was performed to measure and record baseline heart rate and oxygen saturation (SpO2) and baseline blood pressure was recorded. At the beginning of the 6MWT, patient was asked to grade his level of shortness of breath and then to grade his level of fatigue using the Borg scale.
3. Exertion after the 6MWT was evaluated using Borg scale with score of 6 indicated no exertion and 20 indicated maximal exertion **(Borg; 1982)**.
4. The St. George's Respiratory Questionnaire (SGRQ) which is a standardized self-administered airways disease-specific questionnaire developed by (**Jones et al;1991, Jones et al;1992)** . It consists of 136 weighted items, grouped into 12 categories: ambulation (A); body care and movement (BCM); mobility (M); emotional behavior (EB); social interaction (SI); alertness behavior (AB); communication (C); work (W); sleep and rest (SR); eating (E); home management (HM); and recreation (R). Each item was scored from 0 to 10 with a score of 0 indicates no dysfunction, 1-3 mild dysfunction, >3-6 moderate dysfunction, >6-9 marked dysfunction and 10 indicates severe dysfunction and all of the 12 categories are included in an overall Sickness Impact Profile score (SIPS) **(Sullivan; 1988)**.
5. Physiological measurement
    a. Pulmonary function testing using spirometry (Sensor-medics V max series, 2130 spirometer, V6200 Autobox, 6200DL) to estimate the forced vital capacity (FVC; the volume of air that can forcibly be blown out after full inspiration) patient was asked to take the deepest breath he/she can and then exhale into the sensor as hard as possible, for as long as possible. After full inspiration, with the ala of the nose were clipped by fingers, patient was asked to forcibly blown out in one second, to determine the forced expiratory volume in one second (FEV1). Then, the FEV1/FVC ratio was calculated **(Perez 2013)**. Filter mouthpieces was used to prevent the spread of microorganisms.
    b. Arterial blood gases analysis: under complete aseptic conditions and local infiltration anesthesia, an arterial blood sample was taken from the radial, femoral or brachial artery according to availability for estimation of:
        - Partial pressure of oxygen (Pa_{O2}): as a measure of the pressure of oxygen dissolved in the blood and so how well oxygen is able to move from the airspace of the lungs into the blood.
        - Partial pressure of carbon dioxide (Pa_{CO2}): as a measure of the pressure of carbon dioxide dissolved in the blood and so how well carbon dioxide is able to move out of the body **(Fischbach &Dunning; 2009)**.

6- Echocardiographic examination by using available equipment (GE VIVID 7 with 2.5 m Hz tranceducer using standard views.

Respiratory rehabilitation program

The exercise program was formed on the basis of the American Thoracic Society, **(American Thoracic Society; 1999)** recommendations that were basically made out for COPD patients, but they may also be applied to patients with other respiratory disorders. Each patient underwent an intensive (every day for 30 min) inpatient pulmonary rehabilitation program of an average length of 3 weeks (wk), continued later at home for 12 wk for a total program duration of 15 wk. The program consisted of general exercise, performed twice a week for 30 min,

(movements of the thorax, correctional exercise, isometric exercise), respiratory muscle exercise, consisting of 6 series of 5-breath cycles interspersed with 1-min rest periods (altogether 30 breaths), run on Threshold IMP produced by Health dyne Technologies (UK), and bicycle ergometer training, performed once a day for 15 min. The respiratory muscle training and bicycle riding were adjusted to the limits of the patient's tolerance. The timing and intensity of the exercise program was prepared individually for each patient.

Outcome evaluation

Primary outcome was defined as changes from baseline to week 15 in 6MWD with improvement of dyspnea scoring evaluated by MRC and Borg scales and time till exercise intolerance. Secondary outcome was defined as improvement of quality of life (QOL) as measured by St. George's Respiratory Questionnaire (SGRQ).

Statistical analysis

Obtained data were presented as mean±SD, ranges, numbers and ratios. Results were analyzed using Wilcoxon; ranked test for unrelated data (Z-test) and Chi-square test (X^2 test) for inter-group comparisons and paired t-test for intra-group comparisons. Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

The study included 36 IPF patients; 23 males and 13 females with mean age of 64.3±4.7; range: 54-71 years. Mean duration of IPF disease was 6±2.2; range: 2-11 years. Twenty-one patients were overweight with BMI in range of <30 kg/m^2 and 15 patients were obese with BMI>30 kg/m^2 with a mean total BMI of 29.5±1.8; range: 25.3-31.9 kg/m^2. There was non-significant difference between studied groups as regards age, duration of IPF and BMI as shown in table 1.

All patients were WHO-FC range of II-IV; 7 patients of class II, 18 patients were of class III and 11 patients were of class IV with a mean WHO-FC of 3.1±0.7; range: 2-4. All patients were maintained on drug therapy for PAH; 10 patients were maintained on monotherapy, 16 patients on dual therapy and 10 on triple therapy with a mean number of drugs used of 2±0.8; range:1-3. Mean pulmonary artery pressure as measured by echo cardiography was 44.4±7.5; range: 33-58 mmHg. Mean right atrial pressure was 8.7±3.2; range: 4-15 mmHg. Mean cardiac index was 3.25±1; range: 1.7-4.6 L/min/m^2. There was non-significant (p>0.05) difference between studied patients as regards their pre-interventional clinical data, (Table 2).

Baseline exercise performance data showed non-significant (p>0.05) difference between studied groups. All patients showed progressive improvement of their 6MWD throughout the interventional period. At 3-w, the percentage of increase of the distance walked was significantly (p<0.05) longer in group ES and non-significantly (p>0.05) longer in group E compared to group S with non-significantly (p>0.05) higher percentage of increase of distance walked in group ES compared to group E. At 15-w, the percentage of increase of the distance walked was significantly (p<0.05) longer in all groups compared to 3-w percentage of increase and in groups E and ES compared to 15-w percentage of increase in group S with significantly (p<0.05) longer distance at 15-w in group ES compared to group E (Table 3, Fig. 1).

At 15-w, the frequency of patients had MRC= 4 was significantly lower, while the frequency of patients had MRC=2 was significantly (p<0.05) higher in all groups compared to their baseline frequency. Moreover, in groups E and ES, the frequency of patients had MRC=4 was significantly (p<0.05) lower with significantly (p<0.05) higher frequency of patients of MRC=2 compared to 3-w frequency, while the difference was non-significant (p>0.05) in group S (Table 3).

Post-6MWT Borg exertion score showed progressive decrease throughout the interventional period with significantly (p<0.05) higher percentage of decrease at 15-wk compared to 3-wk scores in all groups. At 3- wk, groups E and ES showed significantly (p<0.05) higher percentage of decrease of Borg exertion score compared to group S with non-significant (p>0.05) difference between groups E and ES. On contrary, at 15-wk the inter-group difference was non-significant (p>0.05), but in favor of groups E and ES (Table 3, Fig. 2).

Time till exercise intolerance showed progressive increase in all studied patients throughout the intervention period. All patients showed significant (p<0.05) increase of time till exercise intolerance at 3-wk and 15-wk compared to baseline time with significantly (p<0.05) longer time till exercise intolerance at 15-wk compared to at 3-wk. Time till exercise intolerance at 3-wk was significantly (p<0.05) longer in group ES compared to group S and non-significantly (p>0.05) longer compared to group E. Time till exercise intolerance at 15-wk was significantly (p<0.05) longer in group ES compared to groups S and E, but was non-significantly (p>0.05) longer in group E compared to group S. Percentage of increase of time till exercise intolerance at 3-wk was non-significantly (p>0.05)

higher in groups E and ES compared to group S with non-significantly ($p>0.05$) higher percentage of increase in group E compared to group S. On the other hand, at 15-wk, the percentage of increase of time till exercise intolerance was significantly ($p<0.05$) higher in groups E and ES compared to group S with significantly ($p<0.05$) higher percentage of increase in group E compared to group S (Table 3, Fig. 3).

At 15-wk (end of intervention), mean estimated percentage of FVC and FEV_1 and ratio FEV_1/FVC were significantly ($p<0.05$) higher in all groups compared to their baseline estimates. However, the percentage of increase of both FVC and FEV_1 in group ES was significantly ($p<0.05$) higher compared to groups S and E with non-significantly ($p>0.05$) higher percentages of increase in group E compared to group S (Table 4, Fig. 4).

Baseline estimated Pa_{O2} and Pa_{CO2} levels showed non-significant ($p>0.05$) difference between studied groups. At the end of intervention, estimated Pa_{O2} levels were significantly higher in groups E and ES ($p<0.05$) and non-significantly ($p>0.05$) higher in group S compared to their respective baseline measures. Post-intervention Pa_{O2} levels estimated in group ES were significantly ($p<0.05$) higher, but were non-significantly ($p>0.05$) higher in group E compared to group S with non-significantly ($p>0.05$) higher levels in group ES compared to group E. On contrary, post-intervention estimated Pa_{CO2} levels were non-significantly ($p>0.05$) lower in all studied patients compared to estimated baseline level with non-significantly ($p>0.05$) lower levels in groups E and ES compared to group S and in group ES compared to group E (Table 4).

Baseline QOL scoring showed that all patients were in range of mild-to-moderate dysfunction in all items of the questionnaire with non-significant ($p>0.5$) difference between studied groups as regards individual items and total SIPS. Patients of groups E and ES showed significant ($p<0.05$) improvement of ability to ambulate, while the improvement was non-significant ($p>0.05$) in group S compared to baseline scoring. Emotional behavior and recreation were significantly ($p<0.05$) improvement in group ES, while the improvement of these items was non-significantly ($p>0.05$) improved in groups S and E compared to their baseline scores. All other items of questionnaire were non-significantly ($p>0.05$) improved in studied groups compared to their respective baseline score. Post-intervention SIPS was significantly ($p<0.05$) decreases in all studied groups compared to their respective pre-intervention SIPS. Post-intervention SIPS was significantly ($p<0.05$) decreased in group ES compared to post-intervention SIPS of groups S and E with non-significantly ($p>0.05$) lower SIPS in group E compared to group S. The percentage of change of SIPS as a reflection of improvement of QOL was significantly ($p<0.05$) higher in group ES compared to groups S and E with non-significantly ($p>0.05$) higher percentage of decrease in group E compared to groups S, (Table 5, Fig. 5).

TABLES

Table (1): Patients' demographic data

Data			Group S	Group E	Group ES
Age (years)			65±4 (58-70)	62.5±5 (54-69)	65.3±5 (55-71)
Gender; M:F			7:5	8:4	8:4
Duration of IPF (years)			5.4±1.9 (2-8)	6±2.5 (3-11)	6.5±2.2 (3-10)
Weight (kg)			85±3.6 (79-90)	82.5±4.5 (74-89)	83.8±6 (72-89)
Height (cm)			170±3 (166-178)	167±2.1 (165-171)	169±1.7 (167-172)
BMI (Kg/m^2)	Strata	<30	7 (58.3%)	6 (50%)	9 (75%)
		>30	5 (41.7%)	6 (50%)	3 (25%)
	Mean		29.4±1.7 (27-31.9)	29.6±1.8 (25.3-31.6)	29.4±2.1 (25.5-31.9)

Data are presented as mean±SD, ratio; ranges are in parenthesis

Table (2): Patients' Pre-interventional clinical data

Data		Group S	Group E	Group ES
WHO-FC	Class II	3 (25%)	2 (16.7%)	2 (16.7%)
	Class III	5 (41.7%)	6 (50%)	7 (58.3%)
	Class IV	4 (33.3%)	4 (33.3%)	3 (25%)
Drug combination therapy	Monotherapy	3 (25%)	4 (33.3%)	3 (25%)
	Dual therapy	6 (50%)	5 (41.7%)	5 (41.7%)
	Triple therapy	3 (25%)	3 (25%)	4 (33.3%)
Cardiac echo	PAP (mmHg)	44.4±7.6	45±6.4	43.9±8.9
	RAP (mmHg)	8.6±3.9	9±3.3	8.5±2.4
	CI ($L/min/m^2$)	3.3±1.2	3.2±1	3.25±0.9

Data are presented as numbers & mean±SD; percentages are in parenthesis; WHO-FC: World Health Organization-Functional Class; PAP: pulmonary artery pressure; RAP: right atrial pressure; ; CI: cardiac index

Table (3): Exercise performance measures evaluated at 3 and 15 weeks of intervention compared to baseline measures

Variable				Group S	Group E	Group ES
6MWD (m)		Baseline		313.8±12.1	287±28.1	270±56.7
		3-wk	Distance	325±11.3	304.3±24.4	295.4±53.7
			% of change	3.6±2.2	6.3±3.1	10.1±4.9[b]
		15-wk	Distance	335.8±13.1	319.6±19.5	322.1±46.5
			% of change	7.1±2.3[d]	11.8±5.5[bd]	21.1±10.9[bcd]
MRC	Baseline	MRC 1:2:3		1:7:4	2:5:5	2:6:4
	3-wk	MRC 1:2:3		2:7:3	2:6:4	2:8:2
	15-wk	MRC 1:2:3		2:8:2[a]	3:7:2[ad]	4:7:1[ad]
Borg exertion score		Baseline		14.2±1.7	13.9±1.6	14±1.7
		3-wk	Score	12.2±1.3	11.3±1.1	11.2±1.7
			% of change	13.2±2.5	18.3±4.1[b]	19.4±4.2[b]
		15-wk	Score	10.5±1.3	9.7±0.9	9±1.9
			% of change	25.3±10.9[d]	30.2±4.9 [d]	35.2±13.9[d]
Time till exercise intolerance (min)		Baseline		8.2±0.8	8±0.7	7.9±1
		3-wk	Time	9.7±0.9[a]	10.2±1.1[a]	10.7±0.8[ab]
			% of change	18.7±7.2	27.2±9.3	37.1±23.7
		15-wk	Time	10.9±1[ad]	11.6±1.1[ad]	12.8±0.8[abcd]
			% of change	33.9±6.4	46.1±20.9[b]	64.8±26.7[bc]

Data are presented mean±SD and ratios; a: significant versus baseline measures; b: significant versus Group S; c: significant versus Group E; d: significant versus 3-w measures

Table (4): Pulmonary function tests measured at 15 weeks of intervention compared to baseline measures

Variable		Group S	Group E	Group ES
FVC (%)	Baseline	76.3±5.5	74.8±7	73.7±7
	End of intervention	79.1±5.4[a]	78±7.1[a]	77.8±6.6[a]
	% of change	3.74±1	4.25±1	5.74±1.66[bc]
FEV_1 (%)	Baseline	56.9±4.5	54.1±2.5	54.9±3.8
	End of intervention	59.5±4.7[a]	57±2.6[a]	59.3±3.86[a]
	% of change	4.54±0.83	5.4±1.2	7.93±1.58[bc]
Ratio FEV_1/FVC (%)	Baseline	74.8±5	72.9±7.7	74.8±4.6
	End of intervention	75.4±5.2[a]	73.3±7.8[a]	76.3±4.3[a]
Pa_{O2}	Baseline	64.5±4.6	65.3±3.5	64.9±5.6
	End of intervention	66.3±4.9	69.8±4[a]	70.9±3.4[ab]
Pa_{CO2}	Baseline	29.3±1.2	29.5±1.1	29.2±1.7
	End of intervention	28.7±1.9	28.6±1.5	28.4±1.6

Data are presented mean±SD; a: significant versus baseline measures; b: significant versus Group S; c: significant versus Group E

Table (5): St. George's Respiratory Questionnaire (SGRQ) scoring determined at end of intervention compared to baseline measures

Items		Group S		Group E		Group ES	
		Baseline	End	Baseline	End	Baseline	End
Ambulation		4.5±1	4±0.9	4.7±0.8	3.5±0.9[a]	4.7±0.9	3.7±1[a]
Body care and movement		2.3±0.6	2.1±0.7	2.9±0.9	2.6±1.2	2.4±0.7	2.2±0.8
Mobility		3.9±1.5	3.4±0.7	4.8±1.3	4.4±1.4	4.3±1.1	3.7±0.7
Emotional behavior		4.5±1	4±1	4.3±1.1	3.7±0.8	4.2±0.8	3.3±0.9[a]
Social interaction		2.8±1.4	2.7±1	4.2±0.9	3.7±0.9	4.2±0.9	3.2±1.2
Alertness behavior		4.2±1.1	3.9±1	2.5±1	2.3±0.8	2.3±0.9	2±0.7
Communication		4.2±1.1	3.9±1	3.7±0.9	3.4±1.1	3.7±0.9	3.2±0.8
Work		3.9±1.2	3.7±1.2	3.4±1.3	3.2±1.3	3.4±1.2	3±0.7
Sleep and rest		4.3±1.5	4.2±1.5	4±1.6	4±1.6	4.1±1.6	3.1±0.7
Eating		3.6±1.4	3.3±0.9	3.1±0.8	2.8±0.8	3±0.7	2.9±0.7
Home management		5±1	4.3±1.2	4.2±1.1	4±1.2	4.8±0.9	4.3±0.5
Recreation		5.4±0.9	5.2±0.8	4.8±0.8	4.8±1	5.1±0.8	4.3±0.6[a]
SIPS	Value	49±3.9	44.8±3.9[a]	46.6±3.8	42.3±4.4[a]	46.2±4.1	38.8±2.4[abc]
	% of change	8.5±3.9		9.2±3.2		15.6±5.7[bc]	

Data are presented mean±SD; a: significant versus baseline measures; b: significant versus Group S; c: significant versus Group E

Figures

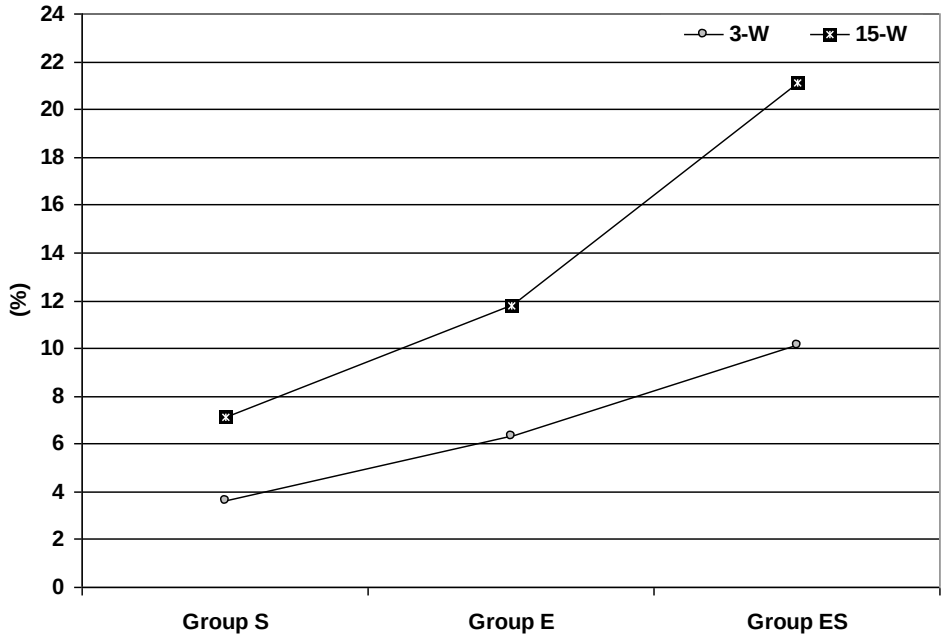

Fig. (1): The percentage of increase of 6MWD of studied groups at 3-W and 15-W of intervention

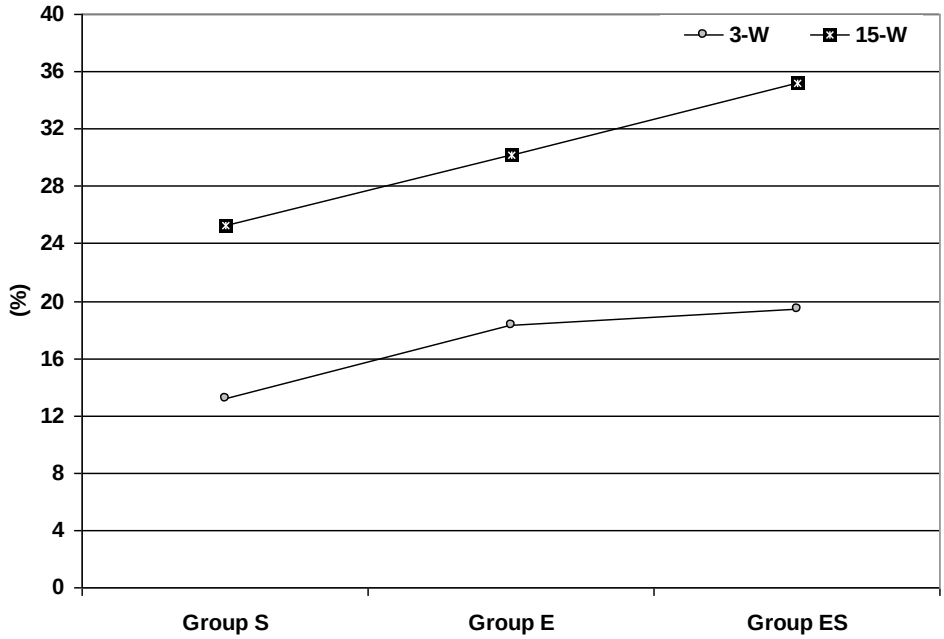

Fig. (2): The percentage of decrease of post-6MWT Borg exertion scoring of studied groups at 3-W and 15-W of

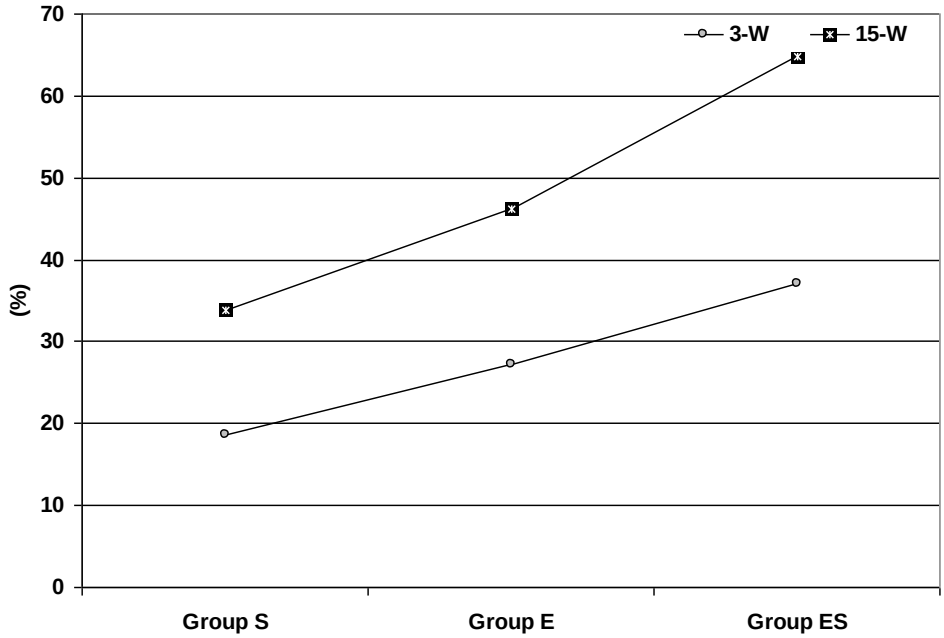

Fig. (3): The percentage of increase of time till exercise intolerance of studied groups at 3-W and 15-W of intervention

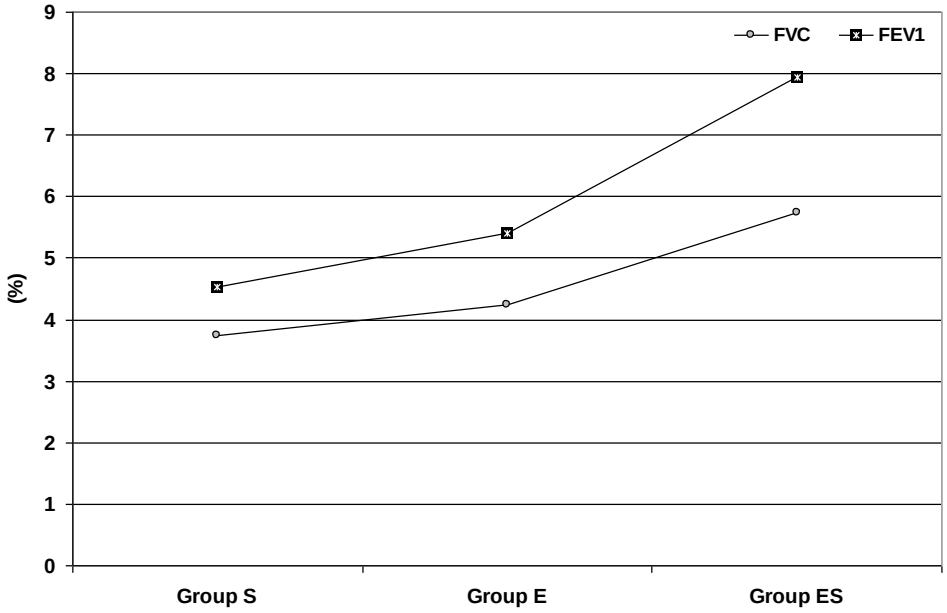

Fig. (4): The percentage of change of FVC and FEV1 at the end of intervention compared to baseline estimates

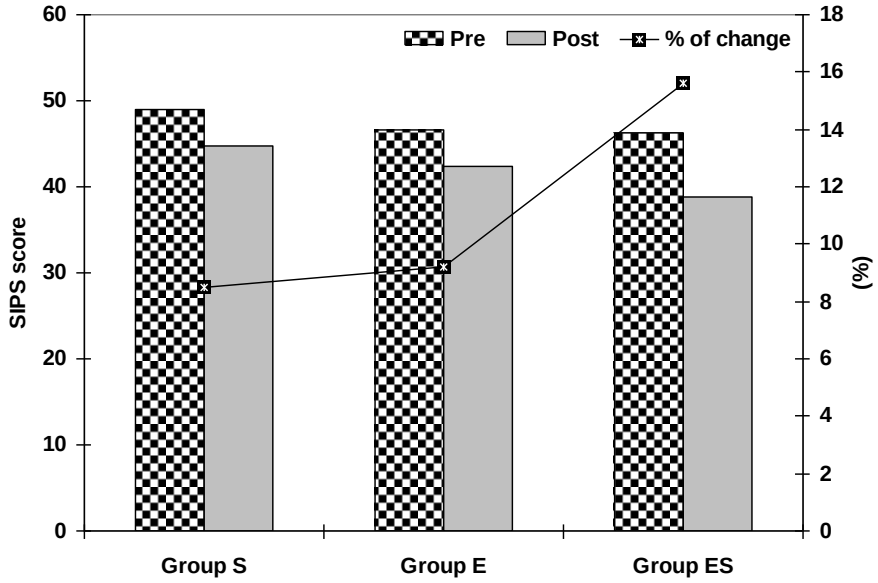

Fig. (5): Mean St. George's Respiratory Questionnaire of studied groups and the percentage of change

Discussion

The current study relied on 6-min walk test (6MWT) as a measure for exercise tolerance and as a mode of easy regular exercise that could be educated to the patient to be trained at home. In support of the choice of this test; **Mainguy et al. (2013)** found that the 6MWT was associated with a lower coefficient of variation between repeated measures and had the best ability to capture changes in exercise capacity supporting its use as an outcome measure in PAH.

The applied interventional program provided multiple beneficial effects manifested as improved patients' frequency in high DI scores and decreased Borg scores of post-exercise exertion. Moreover, the ability and tolerance for exercise were improved as manifested by longer 6MWD and longer time till exercise intolerance. These improvements were reflected on patients' daily life activities as manifested by significant improvement of SIPS on SGRQ scoring with special significant improvement of ability to ambulate. The reported improvement was more evident with exercise alone than with sildenafil alone, and the effect was more manifested in patients received sildenafil and underwent programmed exercise.

In line with data concerned isolated exercise as therapeutic modality; **Mainguy et al.(2010)** reported significant improvement in the 6MWD and the minute ventilation assessed at the same time during cycle endurance test (CET) was decreased by 15% and this was related to improved blood gases measures in idiopathic PAH patients after 12-week rehabilitation program. **Huppmann et al. (2013)** found 6MWD was significantly improved, lung function testing showed marginal improvement of vital capacity and the 36-item short-form QOL questionnaire demonstrated an increase in all eight sub-scores as well as in the physical and mental health summary scores of interstitial lung disease patients performed a standardized pulmonary rehabilitation program. **Becker-Grünig et al.(2013)** reported that patients of congenital heart disease with PAH showed significantly improved mean 6MWD after 3 and 15 weeks of exercise compared to baseline, and QOL, peak oxygen consumption and maximal workload were improved significantly by exercise training after 15 weeks with 100% one- and two-year survival rate and 100% and 93% transplantation-free survival rate after 1 and 2 years, respectively.

Ley et al. (2013) objectively, evaluated the effect of careful exercise training on pulmonary perfusion and blood flow in patients with PAH, as assessed by magnetic resonance imaging (MR) and reported significant increases in mean 6MWD, mean MR flow peak velocity and MR perfusion were significantly greater in the training group compared to control group that showed no significant changes.

Recently, **Ehlken et al.(2014)** reported that exercise training group had significantly better survival rates at 1 and 3 years and less worsening events than the control group maintained on drug therapy without exercise training and this led to lower estimated healthcare costs within a period of 2 years. **Kabitz et al.(2014)** reported that the training program was feasible and well tolerated by PAH patients with excellent compliance and twitch mouth pressure test and 6MWD were increased significantly after 15 weeks of training and concluded that exercise and respiratory training as an adjunct to medical therapy may be effective in patients with PAH to improve respiratory muscle strength and exercise capacity.

The obtained results concerning patients received sildenafil alone or in combination with regular exercise despite being significantly in favor of combination of sildenafil and exercise training point to the efficacy of sildenafil as a therapeutic target in addition to that the patients were maintained on. In support of this assumption; **Zeng et al.(2012)** reported that the 1-, 2-, and 3-year survival rates in patients on sildenafil were 88%, 72%, and 68%, while were 61%, 36%, and 27% in the conventional group with significant difference in favor of sildenafil and concluded that sildenafil therapy was associated with improved survival in patients with idiopathic PAH. **Mainguy et al.(2010)** found sildenafil led to placebo-corrected significant changes in exercise capacity for the 6MWT, the endurance shuttle walk test and CET. **Wu et al.(2013)** through a meta-analysis detected 6 randomized controlled trials and reported that compared with the placebo, sildenafil treatment resulted in fewer hospital admissions, various hemodynamic parameters including mean pulmonary artery pressure were improved, the exercise capacity was improved and the clinical symptoms were relieved based on the breathlessness, fatigue and emotional functioning scores.

Lange et al.(2014) reported that patients with severe PAH due to lung disease may have a survival benefit from targeted therapy composed of endothelin receptor antagonists, sildenafil and prostacyclin analogues compared to untreated patients with less severe PH.

Multiple animal studies tried to explore the mechanisms underlying the beneficial effects of sildenafil and/or exercise on exercise tolerance and pulmonary function test of PAH patients using PAH animal model wherein **Xie et al.(2012)** found early intervention with sildenafil prevented right ventricular (RV) hypertrophy and the development of RV failure (RVF), myocyte T-tubule remodeling, and Ca^{2+} handling dysfunction; however, late treatment with sildenafil did not reverse RV hypertrophy in animals with established RVF, but RV systolic function was improved, both the impairment of myocyte T-tubule integrity and Ca^{2+} handling protein and sarcoplasmic reticulum Ca^{2+} release function were partially reversed. **Rinaldi et al.(2013)** found physical exercise increased mRNA levels of the prostaglandin C-1α and vascular endothelial growth factor genes, which are involved in mitochondrial biogenesis and angiogenesis, and sildenafil dose-dependently promoted both angiogenesis, as shown by increased capillary density, and muscle atrophy, as shown by muscle fibre size and sildenafil-induced effects were more pronounced in trained animals. **Malczyk et al.(2013)** indicated an important role of Classical transient receptor potential-1 protein in pulmonary vascular remodeling underlying the development of hypoxia-induced PH. **Weissmann et al.(2014)** found RV systolic pressure was at the level of healthy normoxic animals, whereas RV

hypertrophy did not benefit from training, but the increase in small pulmonary vessel muscularization was prevented by training and concluded that individualized daily exercise can prevent vascular remodeling in hypoxia-induced PAH.

Conclusion: The obtained results and review of literature allowed concluding that combined exercise training and sildenafil therapy improved exercise tolerance of patients with PAH secondary to IPF with decreased dyspnea and post-exercise exertion and this was manifested as improved quality of life with special regard to ambulation and alleviated disease-induced depression.

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