Original Article

Effects of home-based exercise training on functional outcomes and quality of life in patients with pulmonary hypertension: A randomized clinical trial

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ABSTRACT

Objectives: The objective of this study was to assess the effects of home-based exercise training (HBET) on function and quality of life (QoL) in patients with pulmonary hypertension (PH).
Methods: A prospective, nonblinded, randomized clinical trial was carried out on 84 medically stable patients with PH belonging to any functional class or etiology and of either sex. Patients were randomized to either standard care or HBET. Both groups also received education using the Pulmonary Hypertension Manual (PulHMan). Outcomes included functional capacity from 6-min walk distance (6MWD), QoL using the Medical Outcomes Survey Short Form − 36, functional class (FC), and right heart indices (right ventricular systolic pressure [RVSP] and tricuspid annular plane systolic excursion [TAPSE]) and were assessed at entry and after 12 weeks.
Results: HBET improved 6MWD by 48.5 m and 13 m in the experimental and control groups, respectively ($p < 0.001$). QoL showed statistical improvements after HBET between the groups for the physical and mental components and for the various subdomains (except body pain). Furthermore, FC improved by one grade with HBET ($p < 0.001$).
Conclusion: HBET program improved functional capacity, QoL, and FC in patients with PH.
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1. Introduction

Exercise limitations in pulmonary hypertension (PH) have a profound impact on the morbidity and mortality of patients with PH, for which various physiological systems are responsible.[1] These exercise limitations are the result of a complex interaction between the cardiorespiratory and musculoskeletal systems.[2–4] Considering these limitations and the ability of these dysfunctions to respond to

exercise training, it was hypothesized that participation in exercise training would result in improvements in exercise capacity.

Exercise training in PH has gained popularity over the last two decades. Since the publication of the first randomized clinical trial by Mereles et al,[5] there have been a growing number of published studies and on-going registered clinical trials.[6,7] Recent systematic reviews and meta-analyses have shown demonstrable improvements in function after exercise training.[6,8–11] However, many of the studies included in these reviews are limited by the generalizability of their findings and models of delivery.[11–13] In addition, the use of a home-based model, which has been found to be as equally effective as a supervised exercise program in cardiac rehabilitation,[14] has not yet been studied extensively in PH. One study by Inagaki et al,[15] which studied the effects of an unsupervised 12-week endurance and strength training program on eight patients with group IV PH, found a 33-m improvement in 6-min

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walk distance (6MWD) along with improved quality of life (QoL). Lack of randomized trials with limited studies on heterogenous patients being studied creates the need for a more rigorous methodology with greater generalizability across various etiological groups of PH. This study was therefore aimed at assessing the effects of a 12-week, home-based exercise training program on functional capacity (i.e., 6MWD) and QoL in patients with PH.

2. Methodology

This was a prospective, nonblind, randomized clinical trial, which recruited patients with PH attending a tertiary care university teaching hospital between April 2012 and March 2016. Patients who were diagnosed to have PH (of either sex and any etiology and functional class), stable on medical therapy for three months, and having a tricuspid regurgitant velocity $\geq$ 3.4 m/s with or without right ventricular dysfunction on transthoracic echocardiography were screened for inclusion. Patients with neuromuscular complications limiting rehabilitation, acute coronary events, and/or uncontrolled arrhythmias, undergoing long-term oxygen therapy, or who use home-based noninvasive ventilation were excluded from the study. Participants fulfilling criteria for inclusion and those consenting to participate were included into the study. The university ethics committee approved the study protocol, and all participants provided written informed consent.

A total of 84 patients were enrolled into the study and were randomly allocated to receive standard care (control group) or a structured, therapist-driven, home-based exercise program (experimental group), in addition to standard care, for 12 weeks.

Details of these interventions are provided in the supplemental material. In addition to these interventions, both groups of patients also received a patient education manual – the Pulmonary Hypertension Manual (PulHMan), which has been shown to improve awareness on benefits of exercise in PH.[16] The experimental group received a home-based exercise program that was modified from a program used for patients with heart failure.[17] The allocation was performed by a person from an external source who is not involved in the study and using block randomization of varying block sizes to minimize bias.[18] At entry into the study, a baseline evaluation of demographic parameters and outcomes was performed. Functional capacity was assessed using the 6-min walk test (6MWT) as per the standard recommendations, in which the participant was asked to walk as far as possible in 6 min on a 30-m walk way before assessment, vitals were assessed, and the patient was made to perform the test, after providing detailed instruction and demonstration. Vitals were monitored continuously during the test, and no change to prescribed medications was made.[19,20] Considering the possibility of adverse events during the 6MWT,[21] the test had a therapist walk behind the patient while continuously monitoring all vital signs. QoL and functional outcomes were assessed using the Medical Outcomes Survey Short Form – 36 (SF36) for both physical component score (PCS) and mental component score (MCS) and World Health Organization – functional class (WHO-FC), respectively. Right ventricular function, as determined from tricuspid annular plane systolic excursion (TAPSE) and right ventricular systolic function (RVSP), was assessed from transthoracic echocardiography using standard guidelines[22] and using the GE Healthcare Vivid 7 ultrasound. All echocardiographic
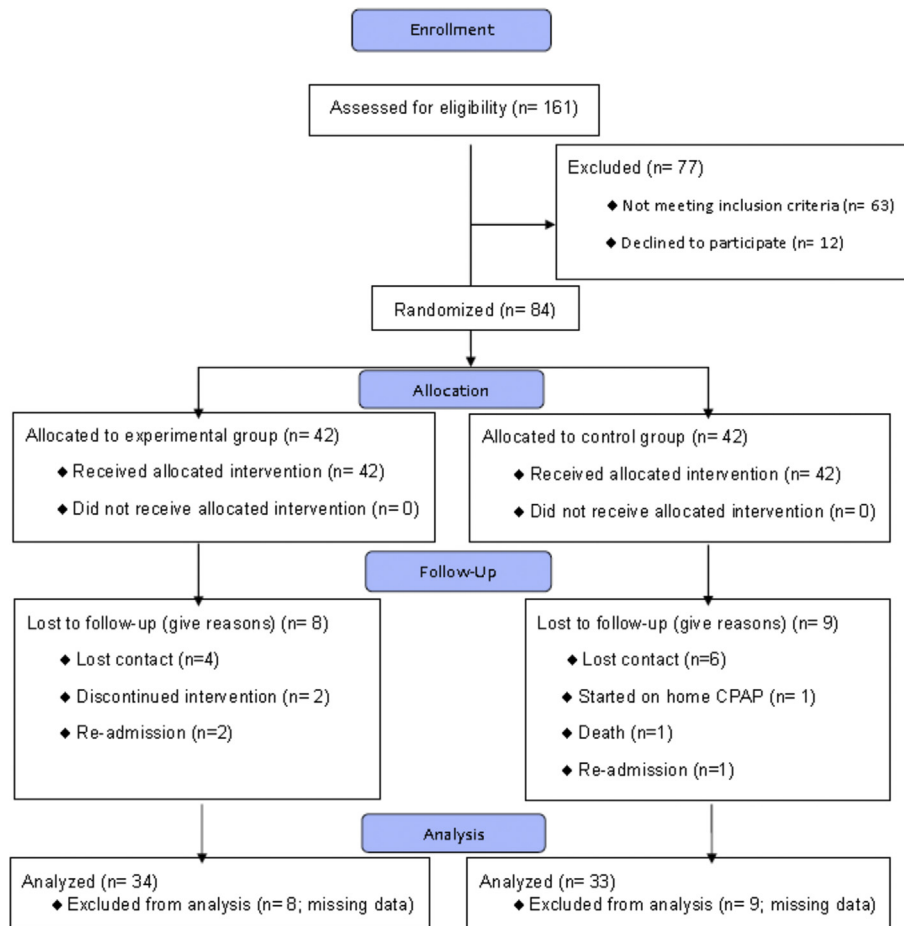

Fig. 1. Flow of participants using the CONSORT flow diagram. CPAP, continous positive airway pressure.

Table 1
Baseline characteristics of participants.

Variable	Control (n = 42)	Experimental (n = 42)
Demographics		
Age in years, mean ± SD	47.28 ± 15.6	51.45 ± 13.7
Male/Female, n (%)	29/13	22/20
Height in cm, mean ± SD	152.8 ± 13.3	150.8 ± 11.9
Weight in Kg, mean ± SD	51.8 ± 14.7	54.4 ± 14.3
BMI in Kg/m^2, mean ± SD	21.9 ± 4.7	23.8 ± 5.4
Group 1, n (%)	17 (40.5)	17 (40.5)
Idiopathic PAH	10 (23.8)	5 (11.9)
Connective tissue disease	0	3 (7.1)
Portal hypertension	1 (2.3)	0
Congenital heart disease	6 (14.3)	9 (21.4)
Group 2, n (%)	5 (11.9)	7 (16.7)
Left ventricular systolic dysfunction	2 (4.8)	5 (11.9)
Valvular disease	1 (2.4)	1 (2.4)
Congenital/acquired left heart inflow/outflow tract obstruction	2 (4.8)	0
Group 3, n (%)	10 (23.8)	10 (23.8)
Chronic obstructive pulmonary disease	5 (11.9)	6 (14.3)
Interstitial lung disease	2 (4.8)	1 (2.4)
Mixed restrictive and obstructive pattern	2 (4.8)	2 (4.8)
Sleep-disordered breathing	1 (2.4)	1 (2.4)
Group 4, n (%)	10 (23.8)	6 (14.3)
Group 5, n (%)	0 (0)	2 (4.8)
Pulmonary hypertension–specific therapies		
Phosphodiesterase 5 inhibitors, n (%)	37 (88.1)	34 (80.9)
Endothelin receptor antagonists, n (%)	4 (9.5)	1 (2.4)
Diuretics, n (%)	41 (97.6)	41 (97.6)
Anticoagulants, n (%)	40 (95.2)	38 (90.4)
Digoxin, n (%)	20 (47.6)	18 (42.9)
Calcium channel blockers, n (%)	4 (9.5)	3 (7.1)
Outcome measures		
WHO-FC, median (IQR)	2 (2, 3)	3 (2, 3)
WHO class I, n (%)	7 (16.7)	4 (9.5)
WHO class II, n (%)	17 (40.5)	16 (38.1)
WHO class III, n (%)	17 (40.5)	21 (50)
WHO class IV, n (%)	1 (2.4)	1 (2.4)
6MWD in meters, mean ± SD	265.8 ± 88.5	277.3 ± 102.1
SF36: PCS	40.6 ± 7.1	40.8 ± 8.3
SF36: MCS	40.4 ± 8.9	42.7 ± 8.6
RVSP in mmHg, median (IQR)	78.5 (65, 105.2)	80 (60, 92.2)
TR velocity in m/s, median (IQR)	4.33 (3.86, 4.9)	4.03 (3.53, 4.52)
TAPSE in mm, mean ± SD	13.85 ± 2.59	14.47 ± 2.88

SD, standard deviation; BMI, body mass index; WHO-FC, World Health Organization – functional class; IQR, interquartile range; 6MWD, 6-minute walking distance; SF36, Medical Outcomes Survey Short Form – 36; RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation.

readings were performed by the same cardiac technologist (>10 years of experience) who was unaware of the group allocation and details of outcome measures. Patients in the intervention arm were provided an exercise log book to ensure they remained adherent to the program (i.e., performed exercises on at least 3 days of the week) for the 12-week duration. All outcomes were reassessed at the end of 12 weeks.

Sample size was determined based on the study by Merles et al[5] and a home-based study on heart failure[17] in the same setting as the present study using the comparison of means to detect a difference of 50 m on the 6MWT. Considering an attrition rate of 30%, the minimum number required in each group was 42, with the study powered at 80% with 95% confidence. Data were analyzed using SPSS, version 22.0. Demographic data were represented according to category of variables (categorical versus continuous) and normality of distribution from the Kolmogorov-Smirnov test. Demographics of all the participants recruited into the study were described using descriptive statistics. Analysis of covariance (ANCOVA) was performed for the outcome measures, considering baseline parameters such as age, sex, and dose of sildenafil and baseline outcomes such as WHO-FC, RVSP, tricuspid annular plane

systolic excursion (TAPSE), 6MWD, and both the physical component scores (PCS) and mental component score (MCS) of the SF36 as covariates. Intention-to-treat analysis was performed, and missing data were assessed for randomness using the Little's missing completely at random (MCAR) test. After establishing data were completely missing at random, multiple imputation method with 20 iterations was performed as recommended.[23]

3. Results

A total of 84 participants were enrolled into the study, of which 67 completed the 12-week home-based exercise training intervention. Fig. 1 demonstrates the flow of participants into the study as defined by the consolidated standards of reporting trials (CONSORT) guidelines.[24] At entry into the study, there were no significant differences between demographic characteristics (Table 1). At the end of 12 weeks, there was a significant improvement in 6MWD by 48.5 m and 13.1 m in the experimental and control groups, respectively ($p < 0.05$) (Table 2). Because there was no difference between the adjusted and unadjusted means, only the unadjusted mean differences with their standard deviations and mean change from baseline for 6MWD, SF36, RVSP, and TAPSE are summarized in Table 2. The adjusted mean differences are reported in the Supplemental B (Tables)

An ANCOVA was run to determine the effect of home-based exercise training on postintervention outcomes (i.e., 6MWD, QOL, WHO-FC, RVSP, and TAPSE) after controlling for various pre-intervention covariates. For 6MWD, there was a statistically significant difference in postintervention 6MWD between the groups ($F (1,67) = 15.257$, $p < 0.001$). The experimental group found an improvement of 48.5 m versus 13 m in the control group ($p < 0.001$). For QOL, there was a statistically significant difference between the groups, with significant changes seen in the experimental group on the postintervention PCS and MCS scores ($F(1,67) = 19.219$, $p < 0.001$ and $F(1,67) = 15.097$, $p < 0.001$, respectively). The difference in PCS and MCS between the groups improved by 5.5 and 4.2 units, respectively. In addition, the mean differences between the groups for the PCS and MCS along with the subdomains also showed significant differences, except for the subdomain of body pain (Table 2).

After exercise training, the postintervention WHO-FC showed a statistically significant improvement between the groups after controlling for various baseline covariates ($F(1,67) = 18.798$, $p < 0.001$). There was however no change in the control group. A statistically significant reduction in median WHO-FC from class III to class II ($p < 0.001$) was seen after exercise training (Table 3). Right heart function, in terms of RVSP and TAPSE, did not show a statistically ($p > 0.05$) or clinically significant change between the groups after exercise training (Table 2).

No adverse events or fatalities were observed during the study. Non–exercise-related adverse events were reported in both the groups and consisted of breathlessness (7/67; 10.4%), vertigo and hemoptysis (1/67; 1.4% each), and lower respiratory infection and warfarin-induced bleed (2/67; 2.9% each). One of the participants with the warfarin-induced bleed in the control group died. Among those who completed the 12-week intervention ($n = 34$), adherence to the program was good (45.2% ± 15.9%) with most of the participants ($n = 26$, 76.4%) completing between 40 and 60% of all exercise sessions. Only a small number (3, 8.8%) completed <40% of all sessions, whereas five (14.7%) were extremely compliant with the sessions, completing >60% of all sessions.

4. Discussion

This is the first home-based exercise training trial from India to demonstrate significant benefits in functional outcomes and QoL.

Table 2
Unadjusted means between groups for all outcome measures after 12 weeks of home-based exercise training.

Outcome	Control (n = 33)	Mean change from baseline	Experimental (n = 34)	Mean change from baseline
6MWD (meters), means ± SD[a]	275.3 ± 93.9	13 ± 39.8 [NS]	334.1 ± 88.4	48.55 ± 44.98[b]
WHO-FC, median (IQR) [NS]	2 (2,3)	−0.6 ± 0.3 [NS]	2 (1,3)	−0.5 ± 0.5 [NS]
SF36-PCS, means ± SD[a]	40.69 ± 8.51	0.07 ± 4.07 [NS]	45.44 ± 8.42	4.59 ± 4.55[b]
SF36-MCS, means ± SD[a]	42.23 ± 8.72	1.75 ± 5.75 [NS]	48.48 ± 6.98	5.75 ± 5.91[b]
Physical function, means ± SD[a]	36.85 ± 10.24	0.68 ± 3.48 [NS]	42.3 ± 9.25	3.08 ± 8.67[b]
Role physical, means ± SD[a]	38 ± 8.31	0.12 ± 4.92 [NS]	44.85 ± 8.72	4.41 ± 8.24[b]
Body pain, means ± SD [NS]	56.53 ± 8.0	−0.18 ± 8.43 [NS]	56.29 ± 7.40	−0.71 ± 11.41 [NS]
General health, means ± SD[a]	33.71 ± 9.81	−0.81 ± 5.63 [NS]	42.23 ± 10.26	6.14 ± 7.19[b]
Vitality, means ± SD[a]	44.43 ± 8.95	2.17 ± 5.78 [NS]	51.33 ± 6.18	7.03 ± 10.28[b]
Social function, means ± SD[a]	38.18 ± 9.51	1.41 ± 6.90 [NS]	44.55 ± 7.71	4.79 ± 11.55[b]
Role emotional, means ± SD[a]	38.86 ± 11.29	0.01 ± 6.71 [NS]	45.54 ± 9.36	3.18 ± 9.03[b]
Mental health, means ± SD[a]	44.06 ± 7.9	1.22 ± 4.66 [NS]	44.68 ± 7.35	3.12 ± 9.83[b]
RVSP (mm Hg), means ± SD [NS]	83.75 ± 29.32	−1.48 ± 4.91 [NS]	75.76 ± 24.95	−3.29 ± 8.03 [NS]
TAPSE (mm), means ± SD [NS]	13.48 ± 2.5	0.12 ± 1.47 [NS]	15.03 ± 2.77	0.28 ± 0.56 [NS]

Abbreviations: 6MWD, six-minute walk distance; MCS, mental component score; NS, not significant; PCS, physical component score; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; WHO-FC, World Health Organization − functional class; SF36, Medical Outcomes Survey Short Form − 36.
[a] $p < 0.05$ between groups.
[b] $p < 0.05$ within groups.

The mean improvement in 6MWD seen was 44 m, which was found to be more than the minimally clinically important difference of 33 m and similar to that observed in a recent clinical trial[25,26] and also in the sildenafil use in pulmonary arterial hypertension (SUPER) trial that assessed the effects of sildenafil in PH.[27] Considering the limited effect of exercise on the RV, the improvements in the 6MWD could be attributed to the impact of exercise on the peripheral muscles which resulted in the improved functional capacity.[28] Exercise training has been found to improve cross-sectional area of the quadriceps and also capillarisation.[29] This could result in improved oxygenation to the exercising muscles and thus improve functional capacity by improving peripheral oxygen consumption.[30−32] Similar improvements in function and QoL have been seen in previous studies.[6,10,11,33]

A 71% reduction in the number of patients in WHO-FC III and a 175% increase in WHO-FC I with home-based exercise training are important findings as patients in lower functional classes are known to have better outcomes in the long term. However, this study did not assess the long-term effects and therefore does not know how it would have had an impact. The improvements seen with long-term sildenafil use are comparable with the improvements seen in this study at the end of 12 weeks.[34] The lack of change in the control suggests that even though medical therapy stabilizes patients, the additional effect of exercise training improved the functional class. Nevertheless, the improvements in WHO-FC could translate to the improvements seen in the 6MWD and SF36 scores.

QoL improved by 4.6 and 5.7 units for PCS and MCS, respectively, when compared between control and experimental groups. These are similar to those described as the clinically relevant scores for improvement in QoL.[35] These could be due to improvement in various factors that may lead to impaired QoL in PH such as dyspnea

and functional limitations, among others.[36] The relevance of both the PCS and MCS was recently studied by Mathai et al[37] in which they found that PCS was significantly associated with survival, whereas MCS was associated with the transplant-free survival period in PH.

Reduction in RVSP with exercise training was observed in this study. However, the small magnitude of change that occurred was not statistically or clinically relevant. This was much lower than what has been observed by Mereles et al[5] with their 15-week exercise training program. RV dysfunction as measured by TAPSE did not improve after exercise training. This is contradictory to what has been seen in young healthy individuals and also in an animal model of chronic obstructive pulmonary disease-induced PH.[38,39] However, the effects of exercise training on TAPSE in PH are yet to be explored.

The exercise program was found to be safe, with non-−exercise-related adverse events being reported. Two fatalities that occurred were not the result of exercise. The safety profile of this study is similar to that reported in an earlier study[40] and also in recent reviews.[6,9] The testing of patients using the 6MWD was also safe. However, considering recent reports on adverse events during the 6MWT,[21] it is advisable to ensure adequate supervision during the test and emphasize safety during exercise prescription.

In addition, the number of participants achieving the minimal clinically important difference (MCID) of 33 m on 6MWT was found to be greater in the experimental groups, with 27 of 34 achieving the MCID as against only 5 of 33 in the control group.

The study is limited by the lack of blinding for functional outcomes, which would influence the Hawthorne effect. Nevertheless, the study provides crucial data on the use of a simple inexpensive rehabilitation model of delivery for exercise training for individuals with PH. In addition, this study brings to light the importance of enrolling patients with PH into an exercise program using a home-based delivery model, especially in countries with limited resources and where geographical barriers prevent participation in supervised rehabilitation programs. Future studies need to assess the dose-response relationship for home-based delivery models and the impact of these programs on physical activity behaviors, dynamic cardiac function, and other biochemical parameters. Methods to improve adherence to home-based programs continue to be a major concern, and methodologies to improve this need to be considered in future trials.

Table 3
Frequency distribution of change in WHO functional class for both groups after exercise training.

WHO-FC	Control		Experimental	
	Baseline (n = 42)	Final (n = 33)	Baseline (n = 42)	Final (n = 34)
Class I, n (%)	7 (16.7)	7 (21.2)	4 (9.5)	11 (32.4)
Class II, n (%)	17 (40.5)	14 (42.4)	16 (38.1)	17 (50)
Class III, n (%)	17 (40.5)	11 (26.2)	21 (50)	6 (17.6)
Class IV, n (%)	1 (2.4)	1 (3)	1 (2.4)	0 (0)

WHO-FC, World Health Organization − functional class.

5. Conclusion

A 12-week, home-based exercise training program improves functional capacity, functional class, and QoL in individuals with PH without any change in right heart function.

Conflict of interest

Funding source

Acknowledgments

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2019.03.002.

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