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Does a structured exercise intervention of at least ten weeksimprove the distance walked in a 6 minute walking test(6MWT) in patients with pulmonary arterial hypertensioncurrently on optimized medical control compared to patientswho do not exercise?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not "Does a structured exercise intervention of at least ten weeks improve the distance walked in a 6 minute walking test (6MWT) in patients with pulmonary arterial hypertension currently on optimized medical control compared to patients who do not exercise?"

STUDY DESIGN: Systematic review of two randomized controlled trials and a prospective case study published between 2006-2013, all English language.

DATA SOURCES: Two randomized controlled studies and a prospective uncontrolled trial which studied the effects of a structured exercise program of at least 10 weeks duration were obtained using PubMed.

OUTCOMES MEASURED: The outcome of each study was the distance (measured in meters) that each patient was able to walk during the 6 minute walking test as compared to their baseline at the beginning of the study. The average of these participants were then used to compare the control group versus the intervention group

RESULTS: Two randomized controlled trials and a uncontrolled prospective study were used in this review. Mereles et al showed a difference between the control and exercise group to be a mean of 111 m (95% CI, 65 to 139; $P<0.001$) after 15 weeks. Chat et al found that there was a statistically significant mean increase of 45m with a 95% CI of 9-80m ($p=0.003$) in the exercise intervention group, and determined the number needed to treat was 3 using dichotomous data. Grunig et al showed a significant mean increase from baseline to 3-week testing (64 +/- 47m, $p<0.001$) and again from baseline to 15-week (71 +/- 35m, $p<0.003$), with no control group studied.

CONCLUSIONS: All three studies demonstrated statistically significant improvement in the distance walked in the six minute walking test after a structured exercise intervention as compared to baseline testing, as well as compared to a control group. A structured exercise intervention in patients with pulmonary arterial hypertension should be considered as a useful addition to medical therapy.

KEY WORDS: pulmonary hypertension, exercise therapy, rehabilitation

INTRODUCTION

While treating patients, it is often difficult to avoid frustration by the patient and the provider when mainstay therapy does not return the patient to the level of function which they desire. This is often the case with pulmonary arterial hypertension (PAH) because it is not curable[1], and the effects on a patient's lifestyle can be devastating. PAH is a chronic sustained elevated blood pressure in the pulmonary arteries, which leads to stiffening of the pulmonary vasculature.[1]

The signs and symptoms of PAH may include dyspnea, chest pain, dizziness, syncopal episodes, fatigue, peripheral edema, and a dry cough.[2] Patients experiencing symptoms at rest indicate severe disease.[2] The New York Heart Association Functional Classes are useful in categorizing patients because of the similarity of the symptoms which are experienced in PAH.[3] The NYHA functional classes are graded from I-IV depending on severity of symptoms.[3] There are several risk factors for developing PAH, including female gender, family history, obstructive sleep apnea, pregnancy, living at higher altitude, certain drugs such as methamphetamines, and other diseases such as congenital heart disease, scleroderma, and lupus.[2] The etiology for patients with PAH include idiopathic PAH, hereditary PAH, or PAH due to diseases that localize to small pulmonary arterioles, such as connective tissue diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis, and drug use.[2]

Although PAH is a relatively uncommon condition, with an estimated prevalence of 12.4 cases per 1 million people in the United States and new diagnoses of 2.3 cases per 1 million, the severity of patient's symptoms generally lead to a long hospitalizations and crippling medical expenses.[4] The average cost for the initial hospitalization for a patient

with PAH was $30,286 with an average length of stay of 11 days.[4] It is often difficult to avoid the initial hospitalization since the condition and diagnosis is unknown to the patient; however, once the diagnosis of PAH is made, proper medical management can help to avoid subsequent admissions. The average cumulative cost per a rehospitalized patient with PAH was $71,622, with an average length of stay of 24.5 days.[4]

The currently accepted therapies for PAH include calcium channel blockers, digoxin, loop diuretics, home oxygen, and Coumadin[2]. Additional medical therapy options include endothelin receptor agonists, phosphodiesterase inhibitors, prostacyclins, and lung transplant in selected patients.[2] Since PAH is not a curable condition, the goal of treatment is to minimize patient's symptoms and reduce the need for hospital readmission. It was previously believed that exercise training would cause an increased risk for sudden cardiac death in patients with PAH due to the sheer force on the pulmonary arteries during exercise; however, recent studies in patients with left sided heart failure have demonstrated the safety of exercise and have broken new grounds in the ability to study exercise interventions in patients with chronic cardiopulmonary disease.[5] This systematic review will utilize two randomized controlled trials and an uncontrolled prospective study evaluating the effect of a structured exercise intervention on distance walked on a 6 minute walking test in patients with pulmonary arterial hypertension currently on optimized medical therapy.

OBJECTIVE

Does a structured exercise intervention of at least ten weeks improve the distance walked in a 6 minute walking test (6MWT) in patients with pulmonary arterial

hypertension currently on optimized medical control compared to patients who do not exercise?

METHODS

This systematic review will study the population of patients that are between the ages of 18-80, who have previously been diagnosed with pulmonary arterial hypertension and are currently on optimized medical therapy. The intervention being reviewed in this study is a structured exercise intervention of at least 10 weeks duration. The comparison group was patients with pulmonary arterial hypertension on current optimized medical control without a structured exercise intervention. The outcome that was measured was the distance walked in the 6MWT after exercise intervention as compared to baseline 6MWT. Two randomized controlled studies were used for analysis, as well as a prospective case study.

The key words used in the searches were "pulmonary hypertension," "exercise therapy," and "rehabilitation." All articles were originally published in peer reviewed journals in the English language. The author searched articles via PubMed and Cochrane library, and articles were selected based on their relevance to the clinical question. Inclusion criteria consisted of studies which were published after 1999. Exclusion criteria consisted of studies which had patients who were under the age of 18 or over the age of 80, or patients who had changed their medications used to control PAH within the previous two months. The statistics of this study were analyzed using mean change from baseline, NNT, p-values and 95% confidence interval.

Table 1 - Demographics & Characteristics of included studies

Study	Type	# of patients	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Merelles, 2006 (5)	RCT, cross over single blinded study	32	18-75 yo	Three months of optimized medical therapy, WHO functional class II-IV	Active lifestyle. Recent syncopal episode. Physical ailment preventing exercise. Medication changes in previous 3 months.	2	Inpatient exercise program for 3 weeks which includes: bicycle ergometer for 10-25 minutes per day, 60 minutes of walking preformed 5 days per week. 5 days per week of 30 minute of resistance training, and 30 minutes of respiratory training Patients continued cardio and resistance training at home for 12 weeks following inpatient stay.
Chan, 2013 (6)	Phase 2b RCT, single blinded	26	21-82 yo	Pulmonary arterial pressure greater than 25 mmHg. WHO functional classes II-III. Optimized medical therapy	Medication change in previous three months. Active lifestyle. Illicit drug use, tobacco use, or pregnancy.	3	24-30 sessions of medically supervised treadmill walking for 30-45 minutes per session over the course of 10 weeks. Target heart rate intensity ranged from 70-80% from baseline maximums. Experimental group also received weekly educational classes.
Grunig, 2012 (7)	Prospective Case Study	22	18-80 yo	WHO Class II-IV, optimized medical therapy	Any change in medication within the previous two months.	1	Exercise therapy consisted of interval bicycle ergometer training at low workloads, mental gait training, dumbbell-training of single muscle groups using low weights (500 to 1000 g) and respiratory therapy 5 days/week. The training was continued at home with at least 30 minutes/day at 5 days/week for the following 12 weeks.

OUTCOMES MEASURES

Two randomized controlled studies and an uncontrolled prospective study were used in this review and the outcome which was measured was patient oriented (POEM). The outcome that was measured for this review was the distance (measured in meters) that each patient was able to walk during the 6 minute walking test with a standard deviation presented as (+/-), as compared to baseline at the beginning of the study. The average of these participants were then used to compare the control group versus the intervention group.

RESULTS

The study conducted by Mereles et al was a prospective randomized trial which consisted of thirty patients with PAH, randomized into a control group (n=15), and a treatment group (n=15). The intervention in this study was a structured exercise intervention of three weeks duration in a hospital, followed by 12 additional weeks of self guided training. The 6MWT was completed pre-intervention, at 3 weeks, and at 15 weeks, and the control group was allowed to cross over to the treatment group at the end of week 15 (n=10).[5]

The initial control group and intervention group did not vary significantly in the 6MWT at baseline. After 3 weeks of treatment, the 6MWT increase was significantly larger in the intervention group (85+/- 56 m) than in the control group (12 +/- 37 m; P=0.0003).[5] After 15 weeks, the 6MWT decreased in the control group (-15 +/- 54 m), whereas patients in the primary training group revealed a further improvement (96+/- 61 m; P<0.0001).[5] The difference between groups was a mean of 111 m (95% CI, 65 to 139; P<0.001).[5] Patients in the crossover group improved similarly to the patients in the initial intervention group, showing a significantly higher increase in the 6MWT after 3

weeks (75 +/- 41 m, $p<0.05$) and after 15 weeks (mean 74 +/- 49 m, $p<0.001$) compared with baseline.[5] Overall, the treatment increased walking distance in the 6MWT by an average of 96 m, an increase of 22%, when combining the data from the primary exercise group and the crossover group.[5] Individual patient data was not available to calculate numbers needed to treat. P-values of less than 0.05 were considered significant. The data in Tables 2-4 is provided from Mereles et al.

Table 2 –Comparison of Control Group vs Exercise Intervention after 3 and 15 weeks [5]

	Baseline 6MWT (m)	3 week 6MWT change from baseline (m)	15 week 6MWT change from baseline (m)
Control (n=15)	411 +/- 86	12 +/- 37	-15 +/- 54
Exercise Intervention (n=15)	439 +/- 52	85 +/- 56	96 +/- 61
p-value	0.38	0.003*	<0.0001*

Table 3 –Mean Difference, Confidence Interval, and P-value for Control vs Intervention[5]

Mean difference after 15 weeks (m)	95% CI (m)	p-value
111	65-139	<0.001*

Table 4 –Crossover Intervention Group Change from Baseline[5]

	3 week 6MWT change from baseline (m)	15 week 6MWT change from baseline
Crossover exercise group (n=10)	75 +/- 41	74 +/- 49
p-value	<0.05*	<0.001*

Chan et all conducted a randomized controlled trial which originally consisted of twenty-six patients, divided into a treatment group (n=10) which received education and a ten week exercise intervention and a control group (n=13) which only received education. The intervention group had three patients eliminated from the trial before analysis of the data, two patients due to changes in medications, and one because of less

than 80% compliance with the exercise regimen.[6] The 6MWT was completed at baseline, and again at week ten.

At baseline, there was no significant difference between the interventional (mean=411 +/- 73m) and control group (377 +/- 97m) in the 6MWT (p=0.183).[6] The intervention group showed a significant increase in distance walked after ten weeks of training to 467 +/- 86m, with a p value of 0.002 compared to baseline.[6] The control group did not demonstrate a statistically significant increase in distance walked, with ten-week results at 389 +/- 107m with a p value of 0.134 as compared to baseline. The difference between the groups was statistically significant, with a mean distance of 45m, 95% CI 9-80m, and a p value of 0.008.[6] Using a significant improvement of greater than or equal to 41m per individual, the results of the study was converted to dichotomous data and was used to measure the numbers needed to treat (NNT=3). The data in Tables 5-7 is provided from Chan et al.

Table 5 – Baseline and 10-week 6MWT data for Control and Exercise Intervention[6]

	Baseline 6MWT (m)	10 week 6MWT (m)	p-value
Control Group (n=13)	377 +/- 97	389 +/- 107	0.134
Exercise Intervention Group (n=10)	411 +/- 73	467 +/- 86	0.002*
p-value	0.183	-	-

Table 6 – Mean Difference, Confidence Interval, and p-value for Exercise Intervention[6]

Mean Difference (m)	95% CI	p-value
45	9-80m	0.008

Table 7 – Calculation of Numbers Needed to Treat[6]

		Relative Benefit Increase (RBI)	Absolute Benefit Increase (ABI)	Number Needed to Treat (NNT)
CER	EER	(EER - CER) / CER	EER-CER	1/ABI
3/13 = 23.1%	6/10 = 60%	1.6	0.369	2.71 = 3 patients

Grunig et al conducted a prospective, uncontrolled trial utilizing the same methods as Mereles et al; however, there was no control group. There were initially 22 patients in the trial; however, one patient dropped out of the study due to an upper airway infection. The baseline average distance walked in the 6MWT was 386 +/- 121m. After 3 weeks, the mean distance walked increased significantly by 64 +/- 47 meters ($P <$ 0.001) and by 71 ± 35 meters after 15 weeks ($P < 0.003$).[7] Only one patient in the trial did not show an increase in distance walked from baseline, likely due to hip osteoarthritis.[7] Nine patients were lost to follow up at 15 weeks, likely due to distance needed to travel to complete the study. Results remained significant after multiple imputations of missing values for the 6MWD at 15 weeks using the predictive mean managing model. The data in Table 8 was taken from Grunig et al.

Table 8 – Mean Distance Walked in 6MWT at Baseline, 3 weeks, and 15 weeks

	Baseline 6MWT Mean (m)	Change from Baseline at 3 week 6MWT (m)	Change from Baseline at 15 week 6MWT (m)
	386 +/- 121	64 +/- 47	71 +/- 35
p-value	-	<0.001*	<0.003*

DISCUSSION

Although each of the three studies in this review demonstrated statistically significant improvements from baseline for patients with pulmonary arterial

hypertension, there were a few factors that may impact the significance of these studies. First, the six-minute walking test has long been thought to be the best test to determine the effectiveness of a medical intervention for patients with cardiopulmonary disease; however, there are a few critics that suggest that the 6MWT is too short in duration to gain any meaningful data for the effectiveness of the trial.[8] Since this review is focused solely on patient oriented outcomes, this criticism was not taken into account when determining significance of this study.

Another factor which should be considered is the multiple etiologies of pulmonary hypertension.[2] These three studies consisted of a heterogeneous group of patient with different etiologies for pulmonary hypertension. Since each of the studies demonstrated significant improvement in the 6MWT in the exercise intervention group, it could be hypothesized that all etiologies of pulmonary hypertension would benefit from an exercise intervention. Also, patients were taken from all functional classes before intervention, thus results cannot be generalized across functional classes.[3] Further studies with homogenous etiologies of pulmonary hypertension should be considered to determine the effectiveness of exercise intervention.

Finally, because of the nature of this intense exercise intervention and the inpatient component of the program, it may be too expensive to safely provide an exercise intervention for patients with pulmonary hypertension. It is likely that insurance companies would not pay for patients to receive long-term inpatient rehabilitation in the United States, as well as paying for maintenance therapy once the initial intervention is complete[6]. If insurance companies will not cover the therapy, it is likely too expensive

for patients to consider exercise intervention as a safe method for improvement of symptoms of pulmonary hypertension.

The results of exercise intervention as compared to pharmaceutical treatment for pulmonary hypertension suggest that exercise intervention may be more effective in improving the 6MWT than drug therapy. In fact, the treatment-related increase in walking distance of 96 m (22%) observed in Mereles et al was higher than the increases observed with the use of sildenafil[9], oral epoprostenol[10], inhaled iloprost[11], and oral bosentan[12].

There were also a few limitations of these studies as well. Because of the nature of the studies, it was impossible to complete a blinded study with the exercise intervention. This could potentially lead to incentive for extra encouragement for the exercise intervention groups. In addition, there was no control group for the study completed by Grunig et al. Finally, each of the studies had small sample sizes, which could have skewed the data. There were only 74 patients combined in this systematic review, with only 28 patients confined to the control groups[5,6,7]. To be sure of these results, future studies should be designed to attract more patients with pulmonary hypertension to participate.

CONCLUSION

The findings of these three studies have demonstrated that there is a statistically significant increase in distance walked in the six-minute walking test from baseline after the conclusion of a structured exercise intervention of at least ten weeks in patients with pulmonary arterial hypertension, currently on optimized medical control compared to patients who do not exercise[5,6,7].

Future studies should be conducted to determine the significance of exercise intervention for individual etiologies of pulmonary arterial hypertension, as well as the effect of exercise intervention on each specific functional class of the disease. There are not any ongoing trials studying exercise intervention in pulmonary arterial hypertension at this time.

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