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Title: The Effect of Eight-week Pulmonary Rehabilitation Program on Dyspnea and Functional Capacity in Patients on Waiting List for Lung Transplantation

Short Title: Is 8-week program enough for lung transplant candidates?

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Abstract

Objectives: The aim of this study was to evaluate the effect of a comprehensive eight-week outpatient pulmonary rehabilitation (PR) consisting of 60-min sessions twice a week under supervision on dyspnea and exercise capacity in patients on the lung transplantation (LTx) candidate.

Materials and Methods: Between March 2012 and December 2014, medical data of 23 patients on the waiting list for LTx who were referred to our pulmonary rehabilitation (PR) unit and completed 16-session outpatient PRP under direct supervision were retrospectively analyzed. Data including exercise capacity as

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assessed by six-minute walking test (6MWT), the rate of perceived dyspnea as assessed by the Borg Scale and Medical Research Council (MRC) Dyspnea Scale were recorded.

Results: Of a total of 23 patients (85%), 57% were males and the mean age was 35±10 (range, 16 to 48) years. Four patients were operated early, as an appropriate donor became available. Diagnosis was as follows: bronchiectasis (n=10, 44%), silicosis (n=7, 30%), sarcoidosis (n=2, 9%), idiopathic pulmonary fibrosis (n=1, 4%), chronic obstructive pulmonary disease (n=1, 4%), and others (n=2, 9%). At the end of the treatment, there was a significant improvement (median 60 m) in the 6MWT scores (360 [70-254] m vs. 300 [139-489] m; p=0.018). A clinical improvement was also observed in the Borg (p=0.000) and MRC scores (p=0.008).

Conclusion: Our study results suggest that an eight-week outpatient PR consisting of training twice a week is effective to decrease perceived dyspnea and to improve exercise capacity in patients who are on the waiting list for LTx.

Keywords: Dyspnea, exercise capacity, lung transplantation, pulmonary rehabilitation, waiting list.

INTRODUCTION

Lung transplantation (LTx) is the only therapeutic option for end-stage chronic lung diseases refractory to maximal medical treatment and is associated with improved quality of life (QoL) and survival [1]. Due to the limited number of donors, LTx candidates may wait for a long period of time on the waiting list [2]. As a consequence, dyspnea and fatigue increases with decreased exercise capacity due to the unpreventable disease progression. Increasing exercise capacity and improving QoL are of utmost importance for a successful transplantation in these patients who are scheduled for a complex surgery [1,3].

In recent years, there is a growing number of publications on pulmonary rehabilitation (PR) and it is recommended in patients with chronic obstructive pulmonary disease (COPD), chronic lung diseases with decreased exercise capacity due to dyspnea and fatigue (i.e., interstitial lung diseases, cystic fibrosis, bronchiectasis, and thoracic deformities) and before and after LTx and lung volume reduction surgery [3-6].

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Although many studies showing the benefits of exercise training in patients with end-stage chronic lung diseases have been published, there is a limited number of studies investigating the efficacy and safety of exercise in patients who are on the waiting list for LTx [6-9].

Physical and emotional preparation of a LTx candidate before surgery may reduce the risk for postoperative complications and improve the patient-centered outcomes [1,10,11]. In addition, such an attempt for well-being may accelerate the postoperative healing and increase survival [12]. In particular, exercise training is essential to optimize functional capacity and crossmatch testing before transplantation and to improve the QoL and patient outcomes after surgery [13]. Although PR is recommended before and after LTx in many transplantation centers, there is no established clinical practice guideline for PR for LTx candidates and recipients [14,15]. In the daily practice, an effective and safe exercise program can be applied based on the physiological alterations of the patients and current exercise training guidelines [15].

In the literature, randomized studies showing the efficacy of the duration of program and number and intensity of sessions under supervision mostly include COPD patients, and there is a limited number of studies on the content and optimal duration of the program in LTx candidates [11,16,17]. Pulmonary rehabilitation programs (PRPs) with a varying content and intensity under direct supervision can be applied in the outpatient or inpatient setting, or a combined approach can be used [18-21]. The content and organization of PRPs substantially vary depending on each country and even on each center in a single country [18,22]. The optimal duration of PRPs has not been well-established yet, and it may range from six weeks to six months [18]. Although a few number of guidelines is available, there is no standard content and optimal duration for PRPs [23,24].

In the present study, we aimed to evaluate the effect of a comprehensive eight-week outpatient-based PRP consisting of exercise training twice a week under direct supervision in our center and home-based training three times a week without supervision on dyspnea and exercise capacity in patients on the waiting list for LTx.

MATERIALS AND METHODS

Between March 2012 and December 2014, medical data of 23 patients who were on the waiting list for LTx and were referred to the PR unit of Training and Research Hospital and who completed eight-week outpatient-based PRP twice a week under direct supervision were retrospectively analyzed. All patients received an individual PRP consisting of physical exercise training and psychological consultation and nutritional intervention. Exercise capacity was assessed using the six-minute walking test (6MWT) at baseline and at Week 8, while the rate of perceived dyspnea was assessed using the BORG Scale and

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Medical Research Council (MRC) Dyspnea Scale at baseline, at the beginning and at the end of each session. In all cases, 6DWMT was performed under oxygen support.

A written informed consent was obtained from each patient. The study protocol was approved by the local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Content of PRP

Clinical Evaluation and Exercise Protocol

All patients underwent clinical evaluation by an experienced pulmonologist in the PR unit and received an education on their disease and treatment options. The patients were also given psychological support to decrease anxiety for LTx surgery. All patients received education on daily practice encouraging healthy behaviors such as regular physical activity, healthy diet, reasonable drug use, compliance to treatment, and disease self-management and psychological support including effective strategies to overcome chronic conditions. The patients who were in need of medical treatment were consulted to a psychiatrist. In addition, training on the utilization of home oxygen delivery systems and inhaled drugs and strategies to overcome dyspnea and relaxation exercises.

Exercise Program

All patients received exercise training twice a week under direct supervision in our clinic. Exercise training included treadmill, cycle ergometer, light aerobic exercises, and upper extremity weight bearing. Each session took 60 min and was supervised by a single physiotherapist. The intensity of training was chosen at 60% of peak heart beat using the 6MWT. During the exercise, oxygen support was delivered through a nasal cannula to maintain an oxygen saturation of $\geq 88\%$. Before and after exercise, the blood pressure was measured and the heart rate was monitored during the exercise. The Borg scale was used before and after each session.

Home-based Exercise Program

In addition to the supervised exercise program which was administered twice a week in the hospital setting, all patients were instructed to perform a home-based exercise program for three days a week. The program included breathing exercises (local expansion exercises, diaphragmatic breathing, and pursed lip breathing), free walking, upper and lower extremity strengthening exercises with thera-band. To ensure that the home-based exercise program was performed, a patient home-based exercise follow-up chart was given to each patient and chart follow-ups on a weekly basis were carried out by the physiotherapist.

Diet

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Each patient received nutritional consulting by the hospital dietician according to the body composition evaluation and nutritional supplements were given, when necessary.

Outcome measurements

6MWT

The 6MWT was conducted in a 30-m corridor in accordance with the American Thoracic Society (ATS) guidelines. The patients were instructed that they should walk as fast as they could. Before and after the test, the Borg fatigue rating and walking distance were recorded [25,26].

MRC Dyspnea Scale

The MRC Dyspnea Scale was used to evaluate perceived dyspnea during daily living activities [27].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 15.0 statistical software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean and standard deviation (SD) and median (min-max), number and frequency. The normality test was performed using the Shapiro-Wilk test. The Wilcoxon test was used to compare pre- and post-exercise results. A *p* value of <0.05 was considered statistically significant.

RESULTS

Of 27 LTx candidates who were referred to our unit, 23 completed the eight-week outpatient-based PRP. Of a total of 23 patients (85%), 57% were males and the mean age was 35±10 (range, 16 to 48) years. Four patients were operated early, as an appropriate donor became available (Figure 1). The distribution of the patients depending on the diagnosis was as follows: bronchiectasis (n=10, 44%), silicosis (n=7, 30%), sarcoidosis (n=2, 9%), idiopathic pulmonary fibrosis (n=1, 4%), COPD (n=1, 4%), and others (n=2, 9%) (Table 1). At the end of the treatment, there was a significant improvement (median 60 m) in the 6MWT scores (360 [70-254] m vs. 300 [139-489] m; *p*=0.018). A clinical improvement was also observed in the Borg (*p*=0.000) and MRC scores (*p*=0.008). The median baseline resting and post-exercise Borg scores were 2 (0-4) and 4 (0-10), respectively. The median post-exercise resting Borg scores were 0.5 (0-3) and the median post-exercise Borg score was 3 (0.5-8) (*p*=0.000 for both). There was also a statistically significant difference in the median pre- and post-exercise MRC scores (*p*=0.008) (Table 2). All patients were using LTOT, only one patient had a history of long-term smoking (COPD patients) and 2 patient had a very short duration of smoking, none of the other patients had used it. There was no serious comorbidities affecting the PRP, because patients who have serious comorbidities before the lung transplantation are evaluated in detail and are usually taken after being excluded.

DISCUSSION

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In the present study, we evaluated the effect of an eight-week outpatient-based PRP twice a week under direct supervision and home-based training three times a week without supervision on dyspnea and exercise capacity in patients on the waiting list for LTx. We found a clinical improvement in the dyspnea scores and exercise capacity in our study population, the median distance in the 6MWT was 300 m (70-524) before the exercise, the median post-exercise value increased to 360 m (60 m increase) ($p=0.018$). We also observed a statistically significant clinical improvement in the perceived dyspnea and rating scores after the exercise.

Dyspnea is a common symptom in lung transplantation candidates who have end-stage lung disease [28]. It has been reported that PR is useful in reducing dyspnea [21] especially inspiratory muscle training significantly improves the dyspnea score of the MRC [29]. Although pre and post-PR median MRC scores were similar in our study, the distribution of scores varied. Thus there was also a statistically significant difference in the median pre- and post-exercise MRC scores ($p=0.008$).

The majority of patients referred to the transplantation centers are COPD patients in the literature [7]; however, our study has remarkable in that almost all patients are non-COPD patients. This can be attributed to the fact that younger patients with a higher life expectancy following transplantation were mostly selected for LTx previously [30]. However, the expected increase in referral to lung transplantation centers of COPD patients has not been achieved. This situation suggests that pulmonologists in Turkey, particularly working in regional hospitals, do not have enough knowledge about the transplantation or do not show the necessary importance [31].

Although there are no established reference ranges for LTx candidates until date, the increase in the 6MWT was higher than the minimal clinically important difference (MCID, 25-33 m) recommended by the American Thoracic Society (ATS) / European Respiratory Society (ERS) [26]. In the literature, studies showing MCID values for an effective PRP have mostly involved COPD patients; however, these values can be used for LTx candidates, as both conditions involve the lungs. Some authors have also advocated that survival rates of these patients considerably increase following transplantation, as evidenced by increased 6MWT scores compared to baseline [1].

Many outpatient-based PRPs which are applied for six to eight weeks twice or three times a week for LTx candidates are compliant to the general recommendations of PR. However, the optimal duration of PRP has not been still established yet, although a minimum eight-week program offers more benefits in the long-term [32]. In the literature, there are also studies showing that eight-week PRP twice a week under direct supervision is not effective [33]; however, the British Thoracic Society (BTS) recommends a six-week exercise program twice a week under supervision [34]. In our study, despite increased distance in the

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6MWT after PRP, they experienced less muscle weakness at the end of the test. Current evidences have also suggested that PRPs may offer greater benefits for the patients who are referred in the early stage of the disease [35].

In a study, Florian et al. [1] showed a significant decrease in the perceived dyspnea scores ($p=0.001$) with a mean increase in the distance of 72 m as assessed by the 6MWT ($p=0.001$) in patients undergoing a 36-week PRP. In our study, we achieved a statistically significant increase in the exercise capacity in the patients undergoing a comprehensive, eight-week (totally 16 sessions) PRP, being relatively shorter than the previous study, which is one of the strengths of our study.

In another study, the effectiveness of a once-weekly supervised PRP with a standard twice-weekly program was compared and once-weekly supervision yielded equivalent improvements in the exercise tolerance as the twice-weekly program [36]. However, the health-related QoL outcomes were poorer for once-weekly supervision in this study. In addition, the aforementioned study did not include transplant candidates. Based on the previous findings and our results, we recommend PRP twice or three times a week under direct supervision to achieve successful results, since LTx candidates may undergo surgery earlier than expected, when an appropriate donor becomes available, and due to the possibility of rapid progression of the disease. Similarly, four patients were operated early and excluded from the study, as an appropriate donor became available. Of these patients, one attended to the PRP for only one week, while the remaining patients received the program for about three to four weeks. Although the duration of PRP and the number of sessions vary depending on the available means of the facility, PRP is recommended for LTx candidates, considering its health benefits before and after surgery [5,6,12,14].

Nonetheless, there are some limitations to this study. First, our sample size was small, and the number of the patients decreased throughout the study. Therefore, we were unable to compare the efficacy of short-term and long-term PRP in our study. Second, we were unable to evaluate emotional aspects and health-related QoL in our study. The QoL was also evaluated using the Short Form-36 and completed at baseline for each patient; however, it was not included in the analysis due to missing data at the end of intervention. We recommend further comprehensive, large-scale, long-term studies to confirm our findings.

The benefits of PRP has not been exactly well-documented in LTx candidates on the waiting list. To date, a few number of studies are available with heterogeneous sampling and non-standardized protocols [1,12,19,37]. Our study is also consistent with the previous studies with similar limitations.

In conclusion, our study results suggest that an eight-week outpatient-based PRP consisting of training twice a week under supervision is effective to decrease perceived dyspnea and fatigue and to

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improve exercise capacity in patients who are on the waiting list for LTx. However, it should be kept in mind that PRP encompasses the whole period until surgery, and patients should be educated on that adherence/compliance to the program would improve the results. Finally, further large-scale, multi-center studies are needed to establish the optimal duration and content of a PRP in LTx candidates.

Ethics Committee Approval: Ethics committee approval was received for this study from the local Ethics Committee of Hospital.

Informed Consent: A written informed consent was obtained from all patients who participated in this study.

Peer-review: None

Author contributions: Concept: L.K.; Design: L.K.,E.P.; Materials: L.K.,E.P.,A.B.,N.D.B.; Data Collection and/or Processing: L.K.,E.P., A.B.,N.D.B; Analysis and/or Interpretation: L.K.,E.P.; Literature Search: L.K.; Writing: L.K; Critical Reviews: E.P., N.D.B

Conflict of Interest: The authors have no conflicts of interest to declare.

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Tables

Table 1. Baseline demographic characteristics of patients

Variable	
Demographics	
Sex, n (%)	
Female	10
Male	13
Age, year (mean \pm SD)	35 \pm 10
BMI, kg/m ² , mean (min-max)	18.8 (13.2 – 26.2)
Diagnosis, n (%)	
Bronchiectasis	10

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Silicosis	7
Others	6
Pulmonary Functions,	
median (range)	
FVC (lt)	1.1 (0.7-2)
FEV1 (lt)	0.7 (0.5-1.4)
FVC%	33 (18-47)
FEV1%	22 (15-43)

Abbreviation: SD, standard deviation; BMI, body mass

index; FVC, forced vital capacity; FEV1, forced expiratory volume in one second.

Table 2. Effects of PRP on dyspnea and exercise capacity

Variable	Before PRP median (min-max)	After PRP median (min-max)	<i>p</i>
6MWT distance (m)	300 (70-524)	360 (139-489)	0.018
MRC (1-5)	4 (2-5)	4 (2-5)	0.008
Borg			
Resting	2 (0-4)	0.5 (0-3)	0.000
Post-exercise	4 (0-10)	3 (0.5-8)	0.000

Abbreviation: PRP, pulmonary rehabilitation program; 6MWT, six-minute walking test; MRC, Medical Research Council.

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Figure 1. Diagram of the study population. Abbreviation: IPF, idiopathic pulmonary fibrosis; COPD, Chronic Obstructive Pulmonary Disease.

