Supplementary Data

Home-based maintenance tele-rehabilitation reduces the risk for AECOPD, hospitalizations and emergency department visits

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Methods and Materials

Inclusion Criteria

Patients fulfilled the following criteria:

1. Written informed consent,
2. Diagnosis of COPD with moderate to very severe airflow obstruction (post-bronchodilator FEV_1 <80% pred.) and a history of AECOPD in the previous year [1],
3. Optimal medical treatment according to GOLD [1] without regular use of systemic corticosteroids,

Exclusion Criteria

Patients were excluded from the study based on the following criteria:

1. Orthopedic, neurological or other complaints that significantly impair exercise tolerance,
2. Respiratory disorders other than COPD,
3. Cognitive reading impairment and/or difficulties to manage electronic devices precluding interaction with the tablet, as judged by the investigator,
4. Patients not on optimal pharmacotherapy.

Primary 2-month PR program

The primary 2-month (8-week) PR program included supervised exercise training consisting of cycling exercise 3 days/week on electromagnetically braked cycle ergometers (Cateye, Ergociser, EC1600; Osaka, Japan). Patients exercised for 45 min by alternating 30-s exercise intervals initially at 100% WR_{peak} with 30-s rest periods. Total workload was increased (by 5%) on a weekly basis. Also the rehabilitation program included resistance training for upper and lower limbs focusing on large muscle groups (e.g.: quadriceps, hamstrings, pectoral etc.) lasting 15 minutes (3 sets X 10 repetitions). Patients were provided with dietary advice by a dietician, instructions on breathing control and self-management techniques by respiratory therapists. The self-management "education" component was considered as vital to enable patients to acquire the knowledge and develop the preservation skills so as to better take charge of the disease.

Post 2-month rehabilitation programs

Immediately after completion of the initial 2-month PR program patients followed either a 12-month home-based maintenance tele-rehabilitation program [home-based tele-rehabilitation group (A): n=47] or a 12-month hospital-based maintenance rehabilitation program [hospital-based rehabilitation group (B): n=50]. Patients recruited to the home-based tele-rehabilitation group performed their own vital sign measurements (heart rate and oxygen saturation) and lung function measurements (spirometry), using a wireless device (MIR Spirodoc, Spirodoc®, Spiro+Oxi, Roma, Italy) fitted with bluetooth technology to transmit the data to a tablet (Lenovo Smart Tab II[7], Bratislava, Slovakia). In addition, patients manually entered onto the same tablet measurements of daily steps captured by a pedometer (Tanita, PD-637 Pedometer, Europe), home exercise vital sign data (oximetry and

heart rate) along with symptoms of dyspnea and leg discomfort (0-10 Borg Scale) as well as responses to questionnaires (HRQoL, CAT, HADS, mMRC). Data were transmitted from the tablet to a web based ICT platform [2] (TELECARE (version 2.2.13): Linkcare Health Services SL, Barcelona, Spain; Singularlogic Integrator S.A., Athens, Greece) via a 3G network (Vodafone Ltd, Athens, Greece). Patients assigned to the hospital-based rehabilitation group visited the hospital twice weekly for 12 months in order to participate to a multidisciplinary maintenance rehabilitation program including exercise training, physiotherapy, dietary and psychological advice.

Home-based maintenance tele-rehabilitation program

Home exercise data were recorded by patients' immediately after completion of the home exercise program and were transmitted to the telemedicine platform on three specific days (every Monday, Wednesday and Friday) every week for 12 months. The rest of the data, namely daily steps, spirometry, oximetry and questionnaires (HRQoL, CAT, HADS, mMRC) were recorded and transmitted twice weekly (every Tuesday and Thursday) for 12 months. Patients were asked also to score the HADS questionnaire and transmit the data once every month. Data were stored on the web-based platform and reviewed regularly (three to four times per week) by the different health care professionals. The home-based tele-rehabilitation program included the following components: a) individualized action plan; b) educational session on self-management; c) physical exercise sessions to remote monitoring; d) access to the call center; e) psychological support; f) dietary advice; g) breathing retraining techniques; h) professional scheduled weekly contacts with a physiotherapist, an exercise scientist, a dietician and a physician via telephone or Skype video conference. Self-management education included skills to boost patient's self-confidence and enable patients to better deal with their own disease (i.e.: early

symptom recognition). Patients were also given instructions to comply with their medications and directions to the respective emergency department in case of necessity.

The home-based maintenance tele-rehabilitation program was comprised by arm and leg exercises, as well as walking drills. Exercises were individually tailored to address each patient's specific requirements and adapted as required by an exercise scientist. The home exercises were taught and practiced during the initial 2-month PR program. In addition, during the 2-month PR program patients and their relatives were taught how to use the tablet and the medical devices for recording and transmitting data and how to log manually data onto the tablet. A video demonstration of the home exercises was installed into the tablet for guiding patients to correctly execute the muscle reconditioning drills.

Home exercise data and step counts, were analyzed by health professionals (using the web based ICT platform) [2] on a frequent basis to provide feedback to patients so as to advance activity levels and exercise training loads. Every week, the training load was advanced according to the patient's symptoms and recorded vital sign parameters. Exercises were individually tailored to address each patient's specific needs and adapted as required by the exercise scientists. Specifically, patients depending on their fitness level judged by their mean daily steps count were divided into three levels (Level A: <2000 steps, Level B: 2000-6000 steps and Level C:> 6000 steps) and were given exercise programs of graded difficulty based on the assessment of their weekly mean number of steps. Patients at home performed three sets of each exercise with one-minute breaks between sets and repetitions (10-12 repetitions). Patients assigned to A Level performed the exercises without weights. Patients assigned to Level B performed the exercises with 0.5 kg weight. Patients assigned to

Level C performed exercises with 1.0 kg weight. After each exercise, patients evaluated their breathlessness and leg discomfort on the 0-10 Borg scale.

The home-based tele-rehabilitation program consisted of 144 sessions performed over 12 months. Each rehabilitation session lasted approximately one hour. Before and after physical exercises patients logged into the tablet information relative to their oxygen saturation and heart rate readings. Patients after completing the exercise session also logged into the tablet scores of dyspnea sensations and leg discomfort (graded according to the Borg scale). An illustrated brochure of prescribed exercises was also provided to each patient before the start of the program. In addition, patients had on the tablet videos installed to follow the sequence of the home exercises drills and breathing retraining techniques, educational leaflets for Chronic Obstructive Pulmonary Disease, information on self-management aspects of the disease, instruction on management of anxiety and depression symptoms in the form of texts, photos and videos. In the case of severe complications, the patient had access to a pulmonologist through a call center.

Hospital-based maintenance rehabilitation program

The 12-month hospital-based maintenance program included aerobic and resistance exercise regimes twice weekly in a similar fashion as they did during the 2-month initial PR program. In addition, patients during the hospital-maintenance program were provided with dietary advice, instructions on breathing control and self-management techniques. The rehabilitation program consisted of 96 sessions performed over 12 months at Sotiria General and Filoktitis Hospitals in Athens.

Usual care

Usual care included optimal pharmacotherapy according to the current GOLD guidelines [1], oxygen therapy in the presence of respiratory failure, vaccination for S.

pneumoniae according to the guidelines, annual vaccination for influenza, and regular follow up by a respiratory physician. Furthermore, the patients were trained in the early recognition of an AECOPD in order to be able to seek for medical care.

Lung function assessment

Tests were conducted by a spirometer (Master Jaeger, Wurzburg, Germany) and included assessment of forced expiratory volumes (FEV_1, FVC), diffusing capacity of the lung ($DL_{,CO}$) and evaluation of static lung volumes (IC, TLC, FRC, RV) (Body Plethysmography System 1085D, MedGraphics Lockbourne, OH US) [3]. The validity of the portable spirometer (MIR Spirodoc, Spirodoc®, Spiro+Oxi, Roma, Italy) was investigated prior to the study by comparing the FEV_1 and FVC values derived from the portable spirometer to those of the spirometer used to assess lung function (Master Jaeger, Wurzburg, Germany) in 6 patients. The two spirometers were mounted in series so as to simultaneously record data. There was minimal disparity in FEV_1 and FVC measurements between the Spirodoc (1.3±0.7 and 3.1±0.6, respectively) and the Jaeger spirometer (1.4±0.7 and 3.3±0.8, respectively) devices.

Exercise capacity

Tests were performed on an electronic ergometer bicycle (Ergometrics 800, Sensor medics, Anaheim, CA, USA) with breath-by-breath gas exchange measurements and cardiac output recordings using impedance cardiography (PhysioFlow, Enduro, PF-07, Manatec Biomedical, France). Patients exercised to the limit of tolerance. The test protocol included: a) a resting period lasting for three minutes, b) a warm-up period lasting for three minutes, during which patients were cycling without load, c) a period of incremental exercise, where patients performed exercise with progressive increasing intensity (5-10 Watt/minute) to the limit of tolerance. The pedaling frequency was set at 50-60 revolutions/minute, while the total

time of exercise did not exceed 10-12 minutes. Throughout the tests, patients breathed through a valve, which was connected to a gas analyzer (Vmax 229, Sensormedics, Anaheim, CA, USA) for recording and subsequent analysis of physiological parameters of breathing (breath-by-breath). Cardiac function was monitored throughout the test by an electrocardiograph of 12 leads (Marquette Max, Marquette Hellige GmbH, Germany), while percentage O_2 saturation (SaO_2%) was recorded with a pulse oximeter (Nonin, PalmSAT 2500, USA).

During the tests patients were connected to a portable cardiographic conduction device (PhysioFlow, Enduro, Manatec Biomedical, Macheren, France), the validity of which has been certified in the past in patients with COPD [4]. Cardiac output (Q) was recorded continuously by the PhysioFlow device. Six electrodes were placed in all subjects, two on the left carotid, two in the breast area and two in the chest area.

Functional exercise capacity was assessed by the 6MWT [5]. Patients marched at their own pace at a desired distance (25m) with a retrograde motion as many times as they succeeded during the period of six minutes [5]. Two tests were performed by the same technician in order to ensure consistency of the results.

Daily physical activity

Daily physical activity measurements were performed by using an Actigraph accelerometer (Actigraph GT3X, Actilife, Pensacola, FL). The Actigraph is a tri-axial accelerometer that allows storage of raw acceleration data. This tri-axial accelerometer is a small and lightweight device adjusted on an elastic belt. It can be worn around the waist above the right hip of the patient. The Actigraph has been validated in patients with COPD [6, 7]. Patients with a minimum of 4 valid days (including weekends), counting only days with at least 480 minutes of wearing time

during waking hours (as defined between 07:00 am-10:00 pm) were contained in the analysis [8]. Vector magnitude units (VMU), the sum of movements in three planes over each minute, were used to quantify the intensity of daily physical activity (i.e., sedentary, light, lifestyle and moderate intensity). Activity data were analyzed by the ActiLife software (version 5.10.0). COPD patients participated in the study exhibited high compliance with the activity monitoring procedure since all of them had at least 4 valid days of measurements. In fact at baseline, the average activity monitor wear time for the home and hospital group was 780±109 and 769±113 minutes per day, respectively, whilst at 14 months was 801 ± 119 and 780 ± 121 minutes per day, respectively. No differences were found in wearing time between the two groups either at baseline or at 14 months follow-up period.

Analysis of adherence rates (compliance)

Adherence to the home-based maintenance tele-rehabilitation and hospital-based maintenance programs was assessed by the adherence rate (actual number of sessions/total expected number of session*100). Adherence was defined in relation to the extent participants complied with the intervention according to recommendations [9]. Adherence to measurements of vital signs, home exercises, responses to questionnaires and daily steps were recorded by the number of registrations entered divided by the number of those recommended, for each participant.

Statistical Analysis

The minimum sample size was calculated based on 90% power and a two-sided 0.05 significance level. The minimum detectable difference in the number of hospitalizations for AECOPD was used for the power calculation, which was obtained from a previous study [10] which evaluated the effect of a PR program on hospitalization frequency during 1 year after completion of the initial PR program

compared with 1 year before PR. Based on the effect size of 0.42 that was calculated from the mean difference (1.37) and SD (3.26) of AECOPD/year (between 1 year after completion of initial PR and 1 year before entry to the study) from the aforementioned study [10] and considering a dropout rate of 20%, a minimum total sample size of 138 patients (46 patients in each group) was estimated to be sufficient to address the study objective. Data are reported as mean and standard deviation (SD) or 95% confidence intervals (CI). The Shapiro-Wilk test revealed that all data were normally distributed. One-way ANOVA was utilized to detect differences among the 3 groups at baseline for all variables. Differences between the home-based maintenance tele-rehabilitation, hospital-based maintenance rehabilitation and usual care groups were investigated by two-way ANOVA with repeated measurements at different time points, namely baseline, 2-months and 14 months after patient entry into the study. Where necessary, significance differences were followed up with pair-wise Tukey's post-hoc analyses. Time to first AECOPD, hospitalization for AECOPD and emergency department visits for each group were evaluated by Kaplan-Meier survival curves and log-rank tests. Poisson regression univariate and multivariate analyses were performed in order to evaluate the influence of the participation in hospital-based PR or home-based tele-rehabilitation programs, AECOPD, hospitalizations for AECOPD and visits to emergency department (ED) in the 1-year of follow-up. Results are presented as hazard ratios (HR) with 95% confidence intervals (CI). Poisson regression univariate and multivariate analyses were additionally performed in order to account for variability in exacerbation rates between patients. Skewed data were logarithmically transformed for regression analyses. P-values <0.05 were considered statistically significant. All tests were two-

tailed. Sample size calculation was performed by GPower 3.1.7 software. Data were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Daily physical activity

Home-based maintenance tele-rehabilitation was equally effective to hospital-based maintenance PR in preserving the initial improvement in time spent (min) in sedentary (by -30±5 min), light (by 38±6 min), lifestyle (by 7±3 min) and moderate (3±1 min) daily physical activities over the 12-month period, and was superior to usual care exhibiting a deterioration in time spent (min) in sedentary (by +11±2 min), light (by -15±3 min), lifestyle (by -4±2 min) and moderate (-3±1 min) daily activities over the same period of time (Figure 3). The fraction of patients who following the initial PR program exhibited an improvement in time spent across the different physical activities was the following: sedentary activity (GROUP A: 55%, B: 58% and C: 18%), light activity (GROUP A: 60%, B: 52% and C: 16%), lifestyle activity (GROUP A: 45%, B: 50% and C: 18%) and moderate activity (GROUP A: 45%, B: 54% and C: 12%).

Adherence/Compliance

The overall compliance rate of the different components of the tele-rehabilitation intervention (Figure 4) over 12-months follow up was 93.5%. In addition patients of the hospital-based rehabilitation maintenance program exhibited good compliance to twice-weekly exercise training sessions corresponding to 91%. No adverse events were reported.

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