Respiratory Medicine 142 (2018) 23–28

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Airway clearance by exercising in mild cystic fibrosis (ACE-CF): A feasibility study

Nathan Ward[a,b,*], Kathy Stiller[c], Hilary Rowe[a], Scott Morrow[a], Judith Morton[a], Hugh Greville[a], Anne E. Holland[b,d]

[a] Adult Cystic Fibrosis Service, Thoracic Medicine, Royal Adelaide Hospital, Chest Clinic, 275 North Terrace, Adelaide, SA, Australia
[b] La Trobe University, Melbourne, Australia
[c] Central Adelaide Local Health Network, Royal Adelaide Hospital, Port Road, Adelaide, SA, Australia
[d] Alfred Health, 99 Commerical Road, Prahran, Vic, Australia

ARTICLE INFO

Keywords:
Cystic fibrosis
Exercise therapy
Respiratory therapy
Physical therapy modalities

ABSTRACT

Background: People with cystic fibrosis (CF) are encouraged to perform airway clearance techniques on a daily basis. Whilst several short-term studies support a potential role for exercise as an airway clearance technique, to date no medium to longer term studies have investigated the use of exercise as a stand-alone airway clearance technique.

Objective: To determine the feasibility of a protocol investigating the use of exercise as a stand-alone form of airway clearance in adults with CF.

Methods: Adults with CF and a $FEV_1 \geq 70\%$ predicted were eligible. After a four week wash-in period of daily positive expiratory pressure (PEP) and exercise, adherent participants were randomised to either daily PEP plus exercise or exercise-only for three months. Pre-specified thresholds for feasibility for the primary outcomes were rates of recruitment ≥30%, randomisation ≥80% and completion ≥80%. Secondary outcomes included respiratory function tests, respiratory exacerbation rate and health-related quality of life.

Results: Of the 57 eligible patients identified, 17 were recruited (30%). After the wash-in period, 13 of the 17 participants (76%) were randomised and all 13 (100%) completed the final assessment. The median (IQR) change in FEV_1 (L) over the intervention period was 0.00 (−0.08 - 0.15) L for the PEP plus exercise group and −0.03 (−0.19 - 0.13) L for the exercise-only group.

Conclusion: The study achieved its a priori target feasibility rates for recruitment and completion but failed to meet the randomisation target rate. Changes in lung function and quality of life were similar between groups. Further refinement of the protocol may be required prior to expansion to a multi-centred trial.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive, life-shortening, genetic condition affecting over 3100 people in Australia [1]. Whilst historically considered a disease of childhood, survival has improved over the last few decades and over 40% of adults with CF in Australia now have normal or only mildly impaired respiratory function as a result of improved therapies [1].

One of the mainstays of treatment for CF is the use of airway clearance techniques (ACTs) to assist with the removal of the characteristic thickened and tenacious respiratory secretions. Most guidelines recommend that people with CF perform these ACTs on a daily basis [2–4]. Exercise is another important component of the therapeutic regimen for people with CF. In addition to its proven cardiovascular and musculoskeletal benefits, some authors have proposed that exercise combined with huffing and coughing may be sufficiently effective to be considered a stand-alone ACT, acting as a substitute for traditional ACTs [5]. Several cross-over studies, involving people with CF, found that exercising on a treadmill significantly reduced the mechanical impedance of respiratory secretions and improved ease of expectoration, probably due to increased ventilation and respiratory flow rates [6–8]. The reduction in mechanical impedance was not seen during stationary cycling, suggesting that the trunk movements seen during walking may be important to facilitate airway clearance. An

* Corresponding author. c/o Thoracic Medicine, 8E032, Royal Adelaide Hospital, Port Road, Adelaide, SA, 5000, Australia,
E-mail addresses: nathan.ward2@sa.gov.au (N. Ward), kathy.stiller@sa.gov.au (K. Stiller), hilary.rowe@sa.gov.au (H. Rowe), scott.morrow@sa.gov.au (S. Morrow), judith.morton@sa.gov.au (J. Morton), hugh.greville@sa.gov.au (H. Greville), a.holland@latrobe.edu.au (A.E. Holland).

https://doi.org/10.1016/j.rmed.2018.07.008
Received 14 May 2018; Received in revised form 10 July 2018; Accepted 16 July 2018
Available online 19 July 2018

uncontrolled trial of 10 children with CF found that substituting a physical activity program for an ACT regimen (i.e. postural drainage, percussion and vibrations) over a 17 day period significantly improved respiratory function [9]. Cerny [10] in a small controlled trial found no differences in FVC and FEV_1 improvement between groups when exercise was used as a substitute for a proportion of traditional ACT sessions during treatment for an acute respiratory exacerbation. However, to date there are no medium to longer term randomised controlled trials evaluating the effectiveness of exercise as a stand-alone ACT. Most consensus guidelines regarding optimal management for people with CF recommend exercise as an adjunct to, but not a replacement for, specific ACTs or do not mention exercise as a form of airway clearance [4,11].

The increased number of treatment options available for people with CF has led to an increase in the complexity and time-burden associated with best practice care [12]. Furthermore, adherence to specific ACTs is lower than for other therapies for people with CF, with as few as 38% of patients doing ACTs as recommended [13]. There are many reasons for non-adherence with ACTs, including feeling well without doing ACTs, insufficient time and the perceived effort and energy required [14]. Of particular interest, previous studies have reported that many people with CF consider exercise as an alternative to specific ACTs, with up to 80% considering exercise as one of their ACTs [15]. In order to provide patient-centred care that minimises treatment burden, acknowledges each person's preferences and maximises treatment outcomes, the role of exercise as a stand-alone ACT needs to be examined in a well-designed clinical trial. The aims of the current study were, for adults with mild CF-related respiratory disease, to: 1) determine the feasibility of a protocol investigating the use of exercise-only versus exercise plus a specific ACT and 2) gather preliminary clinical data on the effect of exercise-only versus exercise plus a specific ACT.

2. Methods

2.1. Study design

This study was a randomised controlled trial comparing exercise-only to exercise plus a specific ACT. Due to variability in the ACT and exercise regimens in routine clinical care, a 4-week wash-in period was incorporated into the study design to ensure participants entered the intervention period after a standardised ACT and exercise routine. This wash-in period was also used to assess adherence with the study protocol, with non-adherent participants withdrawn prior to randomisation. For adherent participants, the wash-in period was followed by randomisation to a 3-month intervention period. Assessments were undertaken prior to the wash-in period (baseline), after the wash-in period (pre-) and after the 3-month intervention period (post-). Recruitment was open for 12 months. The study was approved by the Royal Adelaide Hospital Research Ethics Committee and the La Trobe University Human Ethics Committee and was prospectively registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615001361594). Assessments were performed by assessors who were blinded to group allocation. A data safety management board was convened to review interim data at the midway point of the recruitment period.

2.2. Participants

Adults (≥18 years of age) with a confirmed diagnosis of CF by either a positive sweat test (chloride > 60 mmol/L) or identification of two CF-causing genetic mutations (www.cftr2.org) were recruited from the Royal Adelaide Hospital (RAH) Adult Cystc Fibrosis Service. Inclusion criteria were: mild respiratory disease (i.e. FEV_1 ≥ 70% predicted at baseline assessment), an active patient of the RAH Adult CF Service (i.e. had attended at least 1 appointment in the last 12 months) and clinically stable at the time of baseline assessment (i.e. no new medications for ≥4 weeks prior to baseline assessment, FEV_1 (L) within 10% of most recent value at baseline assessment, no upper respiratory tract infection for ≥ 2 weeks). Patients were excluded if they were: post-lung transplantation, pregnant, unable to understand written English, had a pneumothorax in the last 6 months, haemoptysis > 20 mls in the 4 weeks prior to the baseline assessment, positive culture for Burkholderia Cepacia within the last 12 months, undergoing treatment for non-Tuberculosis Mycobacteria infection or had a condition or abnormality that, in the opinion of the treating CF physician, compromised the patient's safety or would otherwise make them unsuitable for participation in the study.

2.3. Interventions

After completing the baseline assessment, participants underwent a 4 week wash-in period comprising a specific ACT and exercise regimen. Positive expiratory pressure (PEP) was chosen as the specific ACT as it is a commonly utilised ACT and has been shown to be as effective or more effective than other ACTs for clearing respiratory secretions, maintaining respiratory function and preventing respiratory exacerbations [16]. During each PEP session, participants were instructed to perform 6 cycles of 15 breaths per cycle [17]. Participants were also instructed to perform 30 min of moderate to strong intensity (Borg Rating of Perceived Exertion 3–5) exercise daily. Exercise consisted of walking or jogging or alternatively 6 cycles of 5 min of step-ups using an aerobic step, with the height and step rate adjusted to achieve the target exertion intensity. Participants were instructed to perform 2–3 huffs after each cycle of PEP and every 5 min during exercise. Participants' techniques were reviewed at the time of baseline and pre-randomisation appointments. Participants were provided with a Fitbit Charge HR© to promote adherence with the exercise regimen and were sent phone message reminders if the device had not been synchronised with the online platform within the preceding week.

After the 4 week wash-in period participants completed the pre-randomisation assessment where adherence was classified as good (> 5 days/week), moderate (3–5 days/week) or poor (< 3 days/week) based on their self-reported levels of adherence over the preceding week. To be counted as a treatment session, participants needed to report performing at least 4 × 10 breaths for the PEP and 20 min for the exercise components. Participants who reported at least moderate adherence with both the PEP and exercise regimens were then randomised to an intervention group using a computer-generated randomisation sequence to either continue daily PEP plus exercise (control group) or to cease PEP and only use exercise-alone (with huffing) for their ACT (intervention group). The randomisation sequence was concealed using opaque envelopes prepared by investigators not involved in participant recruitment. Participants were not aware of the minimum adherence level required to be randomised. Participants randomised to the intervention period then performed their allocated treatment regimen for three months, receiving a phone call one and two months into the intervention period from one of the investigators to assess and encourage adherence to their allocated treatment regimen and troubleshoot any problems. If a participant experienced a respiratory exacerbation during the intervention phase, participants in the exercise-only group were permitted to commence another form of airway clearance (e.g. PEP) if clinically indicated as determined by their treating physiotherapist for the duration of any additional treatments (e.g. intravenous antibiotics), reverting to their assigned intervention at the completion of the additional treatment.

2.4. Outcomes

Feasibility of the protocol was the primary outcome. Feasibility was defined a priori as: recruitment of at least 30% of eligible patients, randomisation of at least 80% of participants following the wash-in