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Research

Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial

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KEY WORDS

Cystic fibrosis
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ABSTRACT

Question: During an acute exacerbation of cystic fibrosis, is non-invasive ventilation beneficial as an adjunct to the airway clearance regimen? **Design:** Randomised controlled trial with concealed allocation and intention-to-treat analysis. **Participants:** Forty adults with moderate to severe cystic fibrosis lung disease and who were admitted to hospital for an acute exacerbation. **Intervention:** Comprehensive inpatient care (control group) compared to the same care with the addition of non-invasive ventilation during airway clearance treatments from Day 2 of admission until discharge (experimental group). **Outcome measures:** Lung function and subjective symptom severity were measured daily. Fatigue was measured at admission and discharge on the Schwartz Fatigue Scale from 7 (no fatigue) to 63 (worst fatigue) points. Quality of life and exercise capacity were also measured at admission and discharge. Length of admission and time to next hospital admission were recorded. **Results:** Analysed as the primary outcome, the experimental group had a greater rate of improvement in forced expiratory volume in 1 second (FEV_1) than the control group, but this was not statistically significant (MD 0.13% predicted per day, 95% CI −0.03 to 0.28). However, the experimental group had a significantly higher FEV_1 at discharge than the control group (MD 4.2% predicted, 95% CI 0.1 to 8.3). The experimental group reported significantly lower levels of fatigue on the Schwartz fatigue scale at discharge than the control group (MD 6 points, 95% CI 1 to 11). There was no significant difference between the experimental and control groups in subjective symptom severity, quality of life, exercise capacity, length of hospital admission or time to next hospital admission. **Conclusion:** Among people hospitalised for an acute exacerbation of cystic fibrosis, the use of non-invasive ventilation as an adjunct to the airway clearance regimen significantly improves FEV_1 and fatigue. **Trial registration:** ANZCTR 12605000437662. **[Dwyer TJ, Robbins L, Kelly P, Piper AJ, Bell SC, Bye PTP (2015) Non-invasive ventilation used as an adjunct to airway clearance treatments improves lung function during an acute exacerbation of cystic fibrosis: a randomised trial. *Journal of Physiotherapy* 61: 142–147]**

Introduction

Airway clearance is an integral component of the respiratory management of cystic fibrosis (CF).[1] During acute exacerbations of their lung disease, people with CF often find it difficult to maintain effective airway clearance due to increased breathlessness, lethargy and respiratory muscle fatigue.[2] Studies have shown that the addition of non-invasive ventilation (NIV) to a single treatment of physiotherapy techniques for airway clearance assists in overcoming these issues.[3] However, it is not known whether NIV is a beneficial adjunct to physiotherapy treatments for airway clearance if used throughout a hospital admission for an acute exacerbation of CF.

The efficacy of NIV as an airway clearance technique in CF has been examined in several single-session crossover trials. Mucus clearance, as measured by inhaled radioaerosol[4] and expectorated sputum volume,[5–7] was not different with the application of NIV when compared to resting breathing alone[4] or standard chest physiotherapy.[5–7] In addition, there were no differences in lung function, as measured by spirometry, following standard chest physiotherapy and NIV-assisted treatment.[5–8]

However, this does not preclude a role for NIV as an adjunct to airway clearance physiotherapy for people with CF. In several studies, participants reported greater ease of expectoration,[5] less breathlessness[6] and less fatigue[5,7] when standard chest physiotherapy treatment was assisted with NIV. Additionally, participants reported that they preferred treatment with NIV compared to standard chest physiotherapy.[5,6,8] The improvements in breathlessness, fatigue and ease of expectoration may be at least partly explained by the preservation of respiratory muscle strength with NIV-assisted treatment compared to standard chest physiotherapy.[5,6] This effect on respiratory muscle strength suggests that

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people with CF may be able to perform airway clearance manoeuvres with less effort or tolerate more effective airway clearance techniques with the support of NIV, especially when most required – during an acute exacerbation.

Despite the promising results of single-session applications of NIV during airway clearance treatment in people with CF, to date, no study has examined the efficacy of NIV over a longer period of time.[3] Therefore, the research questions for this study were:

1. In adults with moderate to severe CF lung disease and who are admitted to hospital with an acute exacerbation, does the addition of NIV to chest physiotherapy improve the rate of change and discharge values of lung function and subjective symptom severity?
2. Does it improve the change in respiratory muscle strength following chest physiotherapy?
3. Does it improve quality of life, fatigue score, exercise capacity and quantitative sputum microbiology at discharge?
4. Does it reduce the length of hospital admission and lengthen the time to next hospital admission for an acute exacerbation of CF?

Methods

Design

A parallel-group, randomised controlled trial was conducted in two tertiary Australian hospitals with specialist CF units. After signing consent to participate, patients were assigned to the control group (standard comprehensive inpatient care from the CF team) or the experimental group (standard care plus NIV during chest physiotherapy). Group allocation was determined by computer-generated block randomisation, which was stratified for hospital and gender. Randomisation was performed by a person not involved in the study and stored in sealed, sequentially numbered, opaque envelopes, which were opened after the participant had signed consent. The participants, treating therapists and independent assessors were not blinded to treatment group allocation. Participants in the experimental group used NIV during chest physiotherapy from Day 2 of admission until discharge from hospital. Spirometry and subjective symptom severity were recorded daily throughout the admission. All other outcome measures were collected on admission to and discharge from hospital.

Participants, therapists and centres

All patients who were aged over 17 years and admitted with an acute exacerbation of CF to the Royal Prince Alfred Hospital, Sydney, and Prince Charles Hospital, Brisbane, were assessed for inclusion in the study. An acute exacerbation of CF was defined as the need for intravenous antibiotics with the presence of four or more signs or symptoms, according to the criteria used by Fuchs et al.[9] Patients with moderate to severe CF lung disease were included in the study if their forced expiratory volume in 1 second (FEV_1) on admission $< 60\%$ of the predicted value.[10] Patients were excluded from the study if they: were using domiciliary NIV for the treatment of respiratory failure, had precautions to the use of NIV (eg, pneumothorax, recent severe haemoptysis), were colonised with *Burkholderia cepacia* complex, were pregnant or had already participated in the study. The physiotherapy staff rostered to the respiratory inpatient wards applied the interventions after discussion with a senior physiotherapist not otherwise involved in the study.

Interventions

A senior respiratory physiotherapist, who was not otherwise involved in the study, individually assessed all participants and determined the type, frequency and duration of chest physiotherapy treatment with the participant. During chest physiotherapy, all participants performed the active cycle of breathing technique, which consists of cycles of deep breathing, relaxed breathing, huffing and coughing in order to aid mucus clearance.[11] In addition, the physiotherapist determined whether to incorporate any additional techniques, including manual percussion, vibration, postural drainage positioning, autogenic drainage, positive expiratory pressure (PEP) and oscillating PEP.

Non-invasive ventilation treatment

Participants assigned to the experimental group underwent an acclimatisation session on the day of admission. During this time, the appropriate inspiratory and expiratory pressures were determined, and an interface (nasal mask or mouthpiece) was chosen that maximised participant comfort and efficacy (pressure support), whilst minimising leak. On Day 2 of admission, participants assigned to the experimental group were provided with a NIV machine[a] with inbuilt humidifier[b] and were instructed to use NIV during all chest physiotherapy sessions for the rest of their hospital admission. NIV use was recorded with the inbuilt storage card[c] and downloaded at discharge from hospital.

Outcome measures

Spirometry, which was the primary outcome measure, was performed daily to determine the rate of change in FEV_1. Subjective symptom severity was also recorded daily for breathlessness, expectorated sputum volume and energy levels on 10-cm visual analogue scales (breathlessness: 0 = nothing at all, 10 = the maximal I have ever experienced; expectorated sputum volume: 0 = none at all, 10 = as much as I have ever had; energy: 0 = full of beans, 10 = no energy at all). Maximal inspiratory (PImax) and expiratory (PEmax) pressure[12] were measured immediately before and after chest physiotherapy on Day 2 of admission, 1 week after admission and at discharge from hospital. At admission and discharge from hospital, participants also completed the CFQ (a CF-specific quality of life questionnaire),[13] the Schwartz fatigue scale,[14] and the 25-level modified shuttle test to assess exercise capacity.[15] Sputum samples were collected at admission (prior to commencement of intravenous antibiotics), 1 week after admission and at discharge from hospital. Samples were couriered on ice to a central laboratory for quantitative microbiological analysis, which was performed by a blinded assessor. Organisms were identified with the use of standard microbiological techniques, including the API 20 NE system[d] and quantification of pathogens was performed with the use of the modifications of Wong and colleagues.[16] The length of admission and time to next hospital admission for an acute exacerbation[9] of CF were recorded.

Data analysis

The primary outcome measure was rate of change in FEV_1 (% of predicted per day) from admission to discharge from hospital. Data from 10 patients of similar lung function severity (five from each of the hospitals in this study) showed a standard deviation of 0.49% of predicted per day. With an anticipated effect size of 0.5, 17 participants in each group would give 80% power to detect a significant difference ($\alpha < 0.05$) between the two groups. To allow for a 15% dropout rate, we sought to recruit 40 people to the study.

Repeated-measures analyses were performed using linear mixed models to determine if the rates of improvement in FEV_1 and symptom severity were different between the experimental and control groups. The models included fixed effects for *group* (experimental or control), *time* (day of admission), and the *group* by *time* interaction. A random effect for the intercept (ie, the participant) was included. Independent-samples *t*-tests, adjusting for the participants' admission values, were performed to compare the discharge values between the experimental and control groups for FEV_1, symptom severity, quality of life, exercise capacity and quantitative sputum microbiology. Independent-samples *t*-tests were calculated to determine whether there were differences