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The clinical utility of long-term humidification therapy in chronic airway disease

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KEYWORDS

Bronchiectasis;
COPD;
Humidification therapy;
Mucociliary clearance

Summary

Aim: Persistent airway inflammation with mucus retention in patients with chronic airway disorders such as COPD and bronchiectasis may lead to frequent exacerbations, reduced lung function and poor quality of life. This study investigates if long-term humidification therapy with high flow fully humidified air at 37 °C through nasal cannulae can improve these clinical outcomes in this group of patients.

Method: 108 patients diagnosed with COPD or bronchiectasis were randomised to daily humidification therapy or usual care for 12 months over which exacerbations were recorded. Lung function, quality of life, exercise capacity, and measures of airway inflammation were also recorded at baseline, 3 and 12 months.

Results: Patients on long-term humidification therapy had significantly fewer exacerbation days (18.2 versus 33.5 days; $p = 0.045$), increased time to first exacerbation (median 52 versus 27 days; $p = 0.0495$) and reduced exacerbation frequency (2.97/patient/year versus 3.63/patient/year; $p = 0.067$) compared with usual care. Quality of life scores and lung function improved significantly with humidification therapy compared with usual care at 3 and 12 months.

Abbreviations: CON, control group; COPD, chronic obstructive pulmonary disease; ECCS, European Community for Steel and Coal; ECG, electrocardiogram; FEV₁, forced expiratory volume in 1 s; FiO₂, fraction of inspired oxygen; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IC, inspiratory capacity; ICS, inhaled corticosteroids; LABA, long acting beta 2 agonists; LTHT, long-term humidification therapy; LTOT, long-term oxygen therapy; MRC, Medical Research Council; 6MWD, 6min walk distance; PEEP, positive end expiratory pressure; QOL, quality of life; SaO₂, oxygen saturation; SGQR, St George's respiratory questionnaire; TREAT, treatment group.

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Conclusion: Long-term humidification therapy significantly reduced exacerbation days, increased time to first exacerbation, improved lung function and quality of life in patients with COPD and bronchiectasis.

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Introduction

Chronic obstructive pulmonary disease (COPD) and bronchiectasis are both airway disorders characterised by neutrophilic airway inflammation, mucus hypersecretion and retention, and impaired mucociliary transport.^{1–5} Difficulty clearing mucus from the lungs is a feature of both disorders and results in recurrent infective exacerbations and a subsequent decline in lung function and QOL.^{2,6}

A number of treatment strategies to improve mucociliary clearance have been employed. These include physical methods⁷ and mucoactive drugs, such as mannitol, which have been shown to improve mucus clearance and health-related QOL.^{8,9} Recently there has been increasing evidence that humidification therapy may increase mucociliary clearance, reduce mucus viscosity and aid expectoration in airway diseases. Hasani and colleagues demonstrated that as few as 3 h/day of humidification therapy over seven days for bronchiectasis patients significantly increased lung mucociliary clearance measured by radioaerosol labelling.¹⁰ Mall and colleagues demonstrated in a mouse model that airway surface dehydration leads to persistent neutrophilic airway inflammation with increased mucus production and resultant emphysema.¹¹ Taken together, these studies suggest that airway surface dehydration may play an important role in the pulmonary damage associated with chronic airway disorders. However, the effects of long-term humidification therapy (LTHT) in patients with chronic airways disorders are currently unknown.

Thus, the aim of this 12-month randomised study was to examine the effects of LTHT on frequency of exacerbations, QOL, lung function, exercise capacity and airway inflammation in patients with bronchiectasis or COPD, two chronic airway disorders associated with mucus production and recurrent chest infections. Based on the work discussed above, we hypothesised that LTHT would reduce exacerbations and improve physiological outcomes and QOL in patients with chronic airways disease.

Methods

Participants

One hundred and eight (108) patients with COPD or bronchiectasis were recruited from hospital admission or outpatient clinics over the period of a year. The study group represented diverse ethnic groups (Table 1). The study received approval from the local Ethics Committee and was conducted in accordance with the Declaration of Helsinki International Conference on Harmonization (ICH)/Good Clinical Practice, with patients giving written consent.

A clinical diagnosis of COPD was confirmed with spirometry and defined as an FEV₁ of less than 70% of predicted, an FEV₁/FVC ratio < 70% without significant bronchodilator reversibility.¹² Bronchiectasis was confirmed by high-resolution computed tomography (HRCT).¹³ Patients with bronchiectasis associated with cystic fibrosis or hypogammaglobulinaemia were excluded. All patients were

Table 1 Baseline patient characteristics and inflammatory profile.

	TREAT	CON
COPD/bronchiectasis	34/26	29/19
Sex: M/F	31/29	27/21
Ethnicity: E/M/P/O	33/13/12/2	30/6/7/5
Age (yrs)	66.2 (9.5)	69.0 (11)
Respiratory admissions in previous year	0.73 (1.22)	0.58 (1.00)
Non, ex/smoker	16/44	8/40
Pack years	24.6 (20.9)	36 (26.0)
ICS, % ^a	78.3%	85.7%
LABA, %	51.7%	41.7%
Tiotropium, %	13.3%	14.6%
Atrovent, %	21.7%	22.9%
Regular prednisone, %	18.3%	12.5%
Regular, cyclical antibiotics, %	20.0%	12.5%
BMI (kg m ²)	27.8 (5.3)	27.5 (5.9)
Dyspnoea (MRC scale)	2.82 (0.91)	2.86 (0.98)
FEV ₁ (L)	1.17 (0.58)	1.16 (0.42)
FEV ₁ (% of pred)	44.7 (20.7)	45.3 (14.7)
FVC (L)	1.91 (0.70)	2.03 (0.76)
FVC (% of pred)	59.6 (20.1)	62.5 (18.7)
FEV ₁ /FVC (%)	61.3 (18.8)	59.9 (15.9)
IC (L)	1.71 (0.72)	1.72 (0.69)
6MWD (m)	356 (134)	336 (117)
SGRQ symptoms	55.3 (23.0)	57.4 (22.1)
SGRQ impact	39.7 (18.2)	37.2 (18.0)
SGRQ activity	63.7 (20.4)	66.3 (20.2)
SGRQ total score	49.6 (16.0)	49.4 (16.6)
TCC, 10 ⁶ /mg ^b	22.4 (23.3)	18.6 (27.1)
Viability	77.0 (21.2)	78.9 (21.4)
Eosinophil count, % ^b	1.16 (2.52)	2.65 (3.98)
Neutrophil count, %	64.3 (23.0)	66.9 (19.9)
Macrophage count, %	20.4 (8.8)	20.6 (11.2)
Lymphocyte count, %	0.16 (0.44)	0.41 (0.49)

Abbreviations: Ethnicity: European/Maori/Pacific/Other, MRC Scale – Medical Research Council Dyspnoea Scale, 6MWD – 6 min walk distance, SGRQ – St George's Respiratory Questionnaire.

^a % of subjects using the medication.

^b Continuous data are given as mean (SD) except median (IQR).

required to have a history of 2 or more exacerbations in the previous 12 months and daily sputum production greater than 5 ml. Participants were recruited when stable with no sign of an exacerbation for at least 4 weeks. Regular, daily or cyclical, oral antibiotics and prednisone were not exclusion criteria.

All patients were under the care of a respiratory physician at entry into the study and were managed according to best practice Australasian clinical guidelines. Patients started trial treatments once their respiratory status was considered optimal by their respiratory physician.

Study design

This was a prospective, single centre, open labelled, randomised, two parallel group, placebo-controlled trial. Diary cards were used, exacerbations were counted, and patients were also assessed at baseline, 3 and 12 months (Fig. 1).

Outcomes

The primary outcome was the rate of exacerbations per patient over their treatment period. Secondary outcomes included the time to first exacerbation, the number of exacerbated days and hospital admissions, change in QOL measures, lung function, 6 min walk test and inflammatory markers (sputum cell counts) over the 12 months.

Procedures

Patients attended a preliminary assessment visit where spirometry and reversibility were measured. This was followed within two weeks by the first assessment visit (baseline). Medications current at the time of enrolment were recorded but not adjusted nor withdrawn. Dyspnoea was self-rated using the Medical Research Council (MRC) Scale.¹⁴ Vital signs (heart rate and blood pressure) and an electrocardiogram (ECG) were performed at each visit. Spirometry was performed with a MicroLab ML3500 spirometer

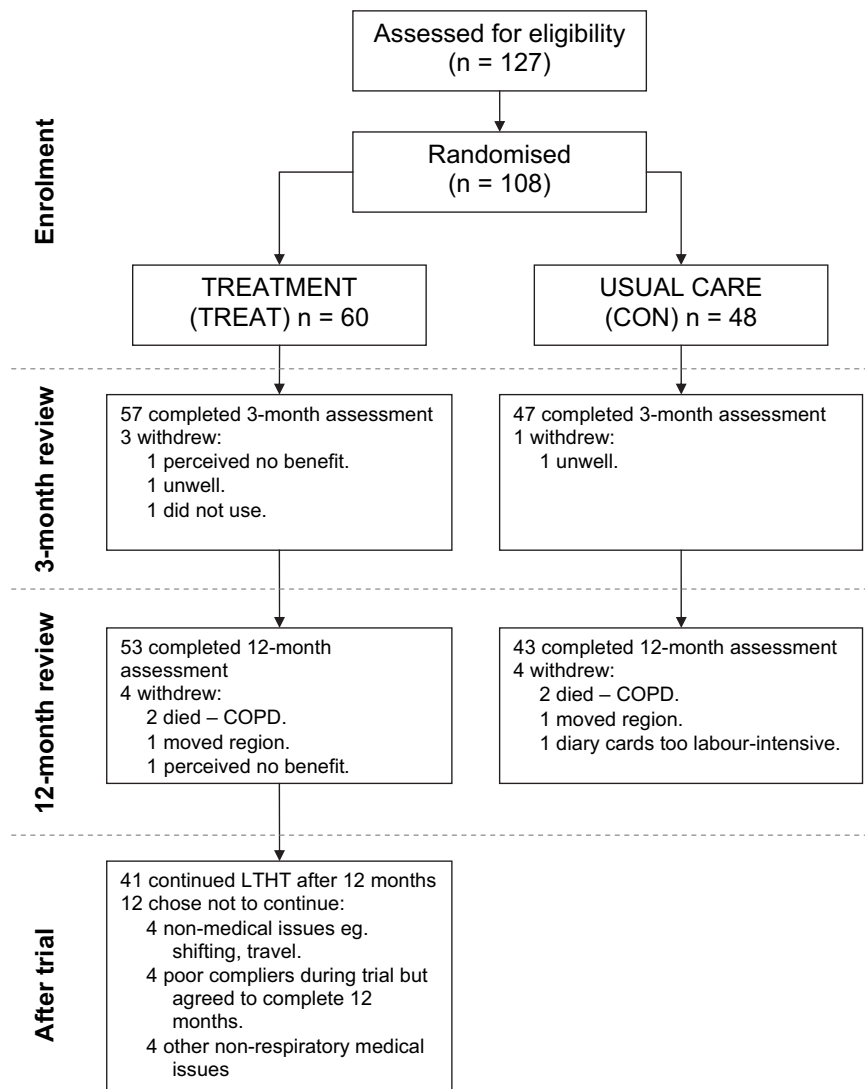


Figure 1 Study design and profile.

(Micromedical) according to ATS/ERS guidelines¹⁵ using European Community for Steel and Coal (ECCS) predicted values.¹⁶ Exercise capacity was assessed with the 6 min walk distance test (6MWD) performed according to ATS Guidelines.¹⁷ Quality of life was assessed with the self-reported St George's Respiratory Questionnaire (SGRQ).¹⁸ Total scores vary from 0 (no disability) to 100 (maximum disability), with a change of 4 units considered to be clinically meaningful.¹⁹ Compliance was measured electronically by the humidification device and the information downloaded at 2-month intervals. A sputum sample was obtained spontaneously if possible, or, if FEV₁ was >30% of predicted, sputum induction was performed and processed according to published guidelines.²⁰

Definition of exacerbations

Exacerbations were event based, and defined as a worsening of 2 or more respiratory symptoms for 2 or more days that required treatment with antibiotics or oral prednisone.²¹ If the period between resolution of symptoms and a further worsening exceeded 7 days, it was considered to be a new exacerbation. Diary cards were examined retrospectively and exacerbations counted by 3 adjudicators blinded to treatment. Hospital admission data were available for the study period and the 12 months preceding the start of the study. Respiratory symptoms (cough, sputum volume, sputum colour and dyspnoea) were recorded by the patients in daily diary cards, assessed using a 5-point Likert scale. These recordings were used to define baseline respiratory symptoms and establish exacerbations based on changes from baseline.

Treatment intervention

Humidified air, fully saturated at 37 °C at a flow rate of 20–25 L/min was delivered via Optiflow™ nasal cannulae connected to a MR880 humidifier and HC210 flow source system (Fisher and Paykel Healthcare, New Zealand) (Fig. 2). This heated pass-over humidifier produces gas phase humidification and has a heated breathing tube to minimise condensation. When used at moderate airflows of approximately 25 L/min, the system delivers positive end expiratory

pressure (PEEP) in the vicinity of 1–3 cm H₂O.²² The PEEP generated is considered to decrease the number of breaths per minute and consequently increase tidal volume and reduce dead space.²³ Patients were instructed to use the equipment for 2 or more hours per day in their home. Two hours was chosen *a priori* by the investigators as a compromise between the short study of Hasani¹⁰ demonstrating mucociliary clearance with 3 h of daily use over one week, and a minimum time period considered reasonable and practical for daily long-term use. Individual flow rates, either 20 or 25 L/min, were set to the flow most preferred by the patient. For patients on long-term oxygen therapy (LTOT), the oxygen supply was connected into the humidified air stream and adjusted so that the patient maintained the same SaO₂. The study was performed in Auckland, New Zealand over a 12-month period encompassing the four seasons of the year.

Statistical analysis

Sample size

Sample size calculation was based on the primary outcome of exacerbation frequency (number of exacerbations per patient per year). Assuming a median rate of 2.92,² a sample size of 50 patients per group was required to achieve 80% power to detect a rate in the intervention group 20% lower than control at the 5% level of significance. The LTHT group size was increased to 60 to potentially account for an increased rate of attrition.

Data analysis

An intention to treat analysis was performed using all available data. The comparison of responses of the two groups (TREAT or CON) was done in the generalised linear model framework, allowing inclusion of demographic variables (gender, ethnic group, age), disease type, number of respiratory admissions in previous year, and pre-treatment covariate where available. Survival analysis of the time to the first exacerbation included the same explanatory variables.

Summary values are expressed using raw (baseline) or model adjusted (least square) means. Results for the exacerbation endpoints are expressed as model predicted

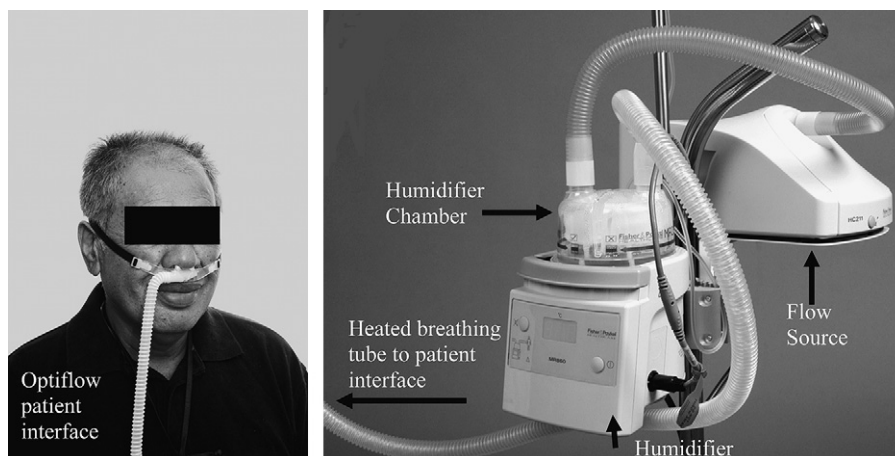


Figure 2 Photograph of LTHT device.

means with 95% confidence intervals. All statistical tests were two-tailed, with a p -value of <0.05 considered as statistically significant.

Results

Patient characteristics at baseline by group are shown in Table 1. The study profile and reasons for withdrawal are given in Fig. 1.

Exacerbations

Exacerbation frequency was 3.63/patient/year in the CON group and 2.97 in the TREAT group ($p = 0.067$), a reduction to 81.8% of control (Table 2). The number of exacerbation days was 33.5/patient in the CON group and 18.2 in the TREAT group ($p = 0.045$) a reduction to 54.3% of control. Similarly, median time to first exacerbation was 27 days in the CON group and 52 days in the TREAT group ($p = 0.0495$) (Fig. 3). More TREAT (12/60 = 20.0%) than CON patients (4/48 = 8.3%) exhibited no exacerbations at all during study ($p = 0.043$). Mean MRC dyspnoea scores were similar between groups at 12 months (TREAT 2.49, CON 2.54, $p = 0.518$), largely unchanged from baseline (Table 1).

Hospital admissions

In the 12 months prior to the study, respiratory-related admissions per year were similar in both groups: TREAT 0.73/year, CON 0.58/year. Results over the study period were TREAT 0.39/year and CON 0.47/year ($p = 0.439$).

Changes in lung function

At enrolment, both TREAT and CON patient groups had moderate to severe impairment, with mean FEV₁ % predicted of 44.7% and 45.3% respectively (Table 1). At 3 months significant differences favouring TREAT were evident for FEV₁, FEV₁ % predicted, FVC and FVC % predicted, and these significant improvements in lung function persisted at 12 months (Figs. 4 and 5). At 12 months FEV₁ had improved by 0.12 L and FVC by 0.28 L. Both FEV₁/FVC ratio and IC were similar for both groups at baseline (Table 1), and did not alter significantly at 3 or 12 months.

Health-related quality of life

The SGRQ total score was similar for both groups at baseline, TREAT 49.6 units and CON 49.4 units respectively, and

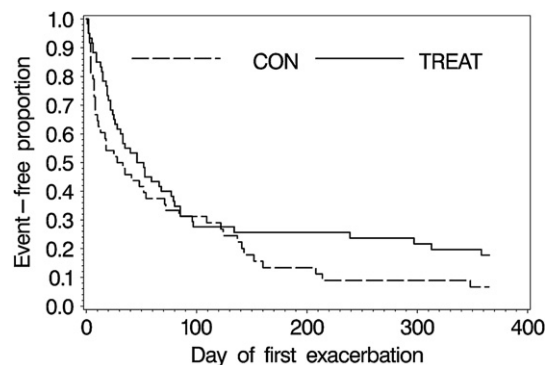


Figure 3 Kaplan–Meier plot for time to first exacerbation.

indicated poor health status (Table 1). At 3 and 12 months the baseline-adjusted symptoms and total score both differed significantly in favour of the TREAT group compared to the CON group (Fig. 5), with all four scores showing differences above 5.9 units at 12 months (symptoms, 8.3; activity, 5.9; impacts, 6.9; total, 6.8).

Changes in exercise capacity

The mean walking distance for the TREAT group decreased by 14.1 m (4.0%) from baseline and by 29.0 m (8.6%) for the CON group ($p = 0.485$). The rate of decline in 6MWD in the TREAT group was inversely correlated with the improvement in FVC over the 12-month study period ($r = 0.31$, $p = 0.03$).

Inflammatory markers

The sputum cell count profile was similar for both groups at baseline, with a neutrophilic predominance (Table 1), and did not alter significantly at 3 or 12 months (data not shown).

Pharmacological therapy

Overall medication use was similar between TREAT and CON groups at baseline, and except for antibiotic use, during the study. Nearly 80% of subjects were on regular ICS, 40–50% on LABA, and 22% on anticholinergic therapy (Table 1). Analysis of both steroid and antibiotic use as recorded by patients on the daily diary cards during the study showed similar rates of prednisone use in both groups, and significantly lower antibiotic use in the TREAT group expressed as the percentage of diary days per patient in which use was recorded (prednisone: TREAT,

Table 2 Exacerbation endpoints.

	TREAT	CON	p -Value	Ratio	95% CI ^b of ratio
Frequency #/patient/year	2.97	3.63	0.067	0.818	(0.660, 1.014)
Annual exacerbation days (geometric mean)	18.2	33.5	0.045	0.544	(0.300, 0.985)
Days to 1st exacerbation (predicted median)	52	27	0.050	0.650 ^a	(0.423, 0.999)

^a Hazard ratio.

^b Confidence interval.

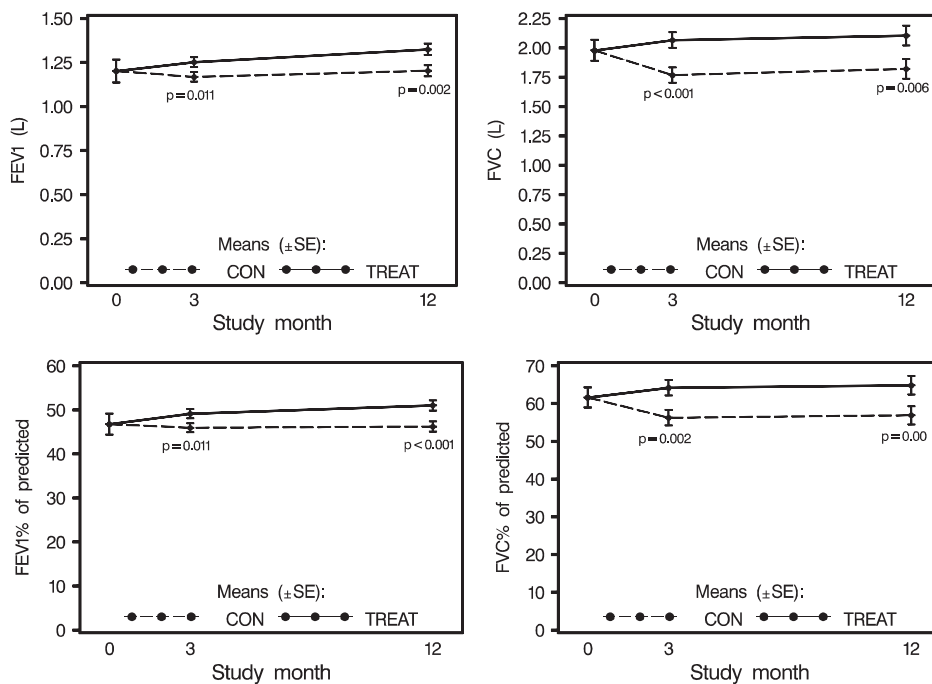


Figure 4 Plots of lung function variables at baseline, 3 and 12 months.

17.7%; CON, 16.0%; $p = 0.765$, antibiotic: TREAT 22.8%; CON, 38.5%; $p = 0.008$)

Compliance

Eighty percent of all TREAT participants (48/60) used the device for an average of at least 1 h/day and 32% (19/60)

used it for at least 2 h/day. The mean use/day/patient was 1.6 h (SD = 0.67).

Adverse events

No serious adverse events defined as ocular, oropharyngeal, cardiac, respiratory, gastrointestinal, or dermatological

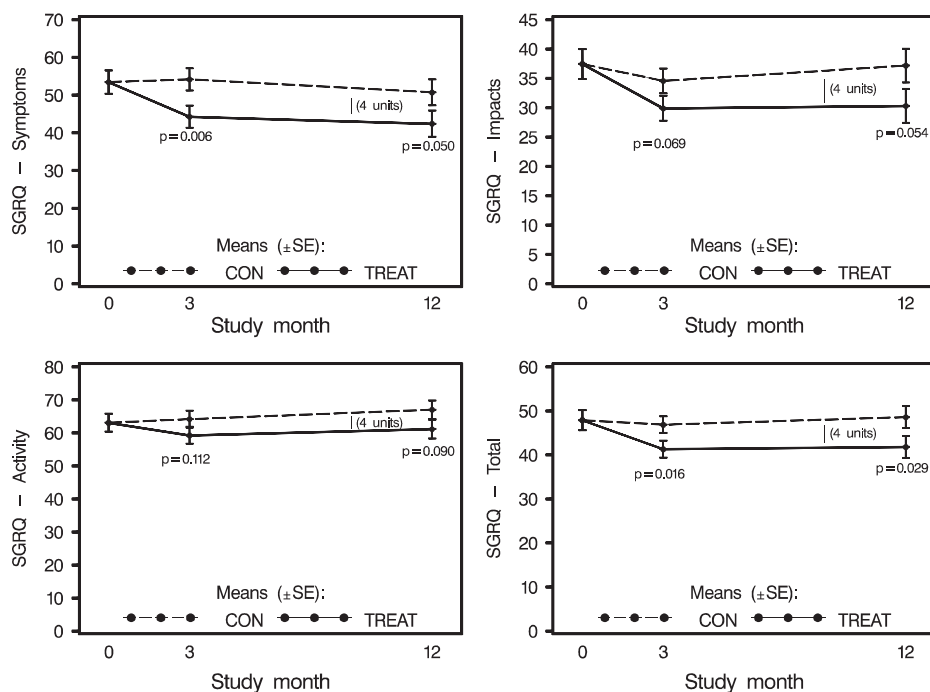


Figure 5 Plots of quality of life variables at baseline, 3 and 12 months.

side effects related to the therapy were reported during the study.

Patient satisfaction

When questioned at study completion, 41 (77%) patients of the remaining 53 in the TREAT arm (see Fig. 1) were satisfied with LTHT therapy and wished to continue using it daily. For the 12 patients not wanting to continue there were three reasons: poor compliance during the trial but agreed to complete only the 12 months trial period ($n = 4$); non-medical issues impacting compliance, e.g. shifting location ($n = 4$), and non-respiratory medical issues affecting compliance ($n = 4$).

Discussion

This is the first study examining the long-term effects of high flow humidification therapy in patients with bronchiectasis and COPD. Although a previous study has shown one week of high flow humidification therapy could improve lung mucociliary clearance in bronchiectatic patients, it was unknown whether LTHT would be tolerated, complied with, and ultimately efficacious in a compromised population with chronic airways disease. Our data demonstrate that averaging as little as 1–2 h/day of LTHT decreased the number of exacerbation days and increased the time to first exacerbation. Significant improvements were also noted in lung function and QOL scores with LTHT. In the discussion that follows we assess the impact of these findings, examine potential mechanisms of action of LTHT, and explore the limitations in our study design.

LTHT is an effective treatment for chronic airways disease

While LTHT reduced two clinical aspects of exacerbations, namely the number of exacerbation days and the time to first exacerbation, it did not quite significantly reduce the exacerbation frequency, the primary outcome ($p = 0.067$). However, given the strong trend favouring LTHT (2.97 versus 3.63 events/year) we posit that the study was slightly underpowered for this outcome, for several reasons. Firstly, we observed a slightly lower (18.2%) than anticipated reduction (20% was used in sample sizing) in exacerbation frequency with LTHT treatment. Secondly, losses to follow-up were similar for the two treatment groups, but higher than anticipated for the CON group, resulting in imbalance that affected study power. Lastly, and perhaps most importantly, whereas exacerbation frequency is considered to be a key outcome measure in the clinical assessment and management of patients with COPD and bronchiectasis, it is an extremely difficult endpoint to measure accurately. Several recent commentaries, and our own experience, have highlighted the pitfalls associated with quantifying exacerbation frequency and severity.^{24,25} Thus the sample size calculated *a priori* for exacerbation frequency from published data may have been underestimated. In the context of significant improvements noted in the number of exacerbated days, time to first exacerbation, lung function and QOL, we consider that the

strong trend in reduced exacerbation frequency is consistent with a therapeutic benefit of LTHT in patients with chronic airways disease. This is also supported by the analysis showing lower TREAT group antibiotic use ($p = 0.008$) as recorded on the diary cards used in determining exacerbations.

The results found with LTHT are also quantitatively similar to previous reports using medical therapy in patients with chronic airways diseases. For example, inhaled corticosteroids (ICS), a mainstay of airway treatment, alone or in combination with long acting beta 2 agonists (LABA), and the long acting anticholinergic bronchodilator, tiotropium, have been shown to reduce exacerbation rates by 15–25%, decrease the rate of decline in lung function, and improve QOL significantly in patients.^{26,27} The reduction in exacerbation rate by 18.2% with LTHT in our study is within this range of improvement seen with best practice medical therapy. Furthermore, the significant improvements in FEV₁ reported here are similar to that achieved with combination inhaler therapy in patients with COPD.²⁶

Mechanisms of action of LTHT

There are several mechanisms by which LTHT may improve outcomes in chronic airways disease: LTHT may cause a decrease in airway inflammation. Sputum cell counts, however, did not alter over time in either the TREAT or CON groups, suggesting that LTHT was unlikely to reduce airway inflammation. Consistent with the short-term humidification study of Hasani¹⁰ LTHT may lead to improved outcomes through enhanced lung mucociliary clearance. This is supported physiologically by the parallel improvement in FEV₁ with FVC in the treatment group, without change in the FEV₁/FVC ratio. This suggests that LTHT may improve small airway function and reduce lung gas trapping by improving mucociliary clearance. Other possibilities include the mechanical effects of PEEP which slows down the rate of breathing, and airflows of 20–25 L/min which may improve gas exchange by providing washout of dead space.^{28,23} However within the context of the current treatment trial, insights into mechanisms by which LTHT can improve outcomes remain speculative.

Limitations of study

Although there are unavoidable limitations to the current treatment study, there are also strengths that should be acknowledged. The therapy occurred over a continuous 12-month period, was tested against a control of 'standard care', and was reported with an intention to treat analysis. The use of three blinded assessors for adjudicating exacerbations avoided bias, and the statistical analysis of exacerbation rate was implicitly time-weighted, providing conservative estimates.²⁴ Assessments were made at both 3 and 12 months, demonstrating repeatable and sustained improvements in outcomes.

Nevertheless, there are also several potential weaknesses in the study. Firstly, there could not be a placebo treatment indistinguishable from LTHT. Sham (placebo) humidification therapy for the usual care group was considered, but no placebo therapy could be designed that

was undetectable to the patient. A system consisting of high flow nasal delivery of 37 °C air at ambient humidity levels without water vapour added was considered likely to have a detrimental effect on patients by drying their upper airways.

Secondly, active treatment compliance did not meet the initial design goals. It averaged 1.6 h/day rather than the expected 2 h/day over the 12-month treatment period. Compliance time per day is a factor in a 12-month study. Tsolaki and colleagues found 45% of patients offered treatment refused to commit to 5 h non-invasive ventilation treatment per day over a year.²⁹

A third possible limitation to our study was the inclusion of patients with either COPD or bronchiectasis. Although COPD and bronchiectasis are two distinct disorders with different aetiologies, they have similarities: both are chronic airway disorders characterised by neutrophilic inflammation and increased mucus secretion. Furthermore, patients with COPD may have co-existent bronchiectasis, noted to be 29% in one study.³⁰ For entry into this study patients needed to have symptoms of two or more exacerbations in the previous year, and also be producing >5 mL of sputum per day. The rationale was that LTHT would improve mucociliary clearance for both patient groups, resulting in improved patient outcomes. Since the trial was not designed for subgroup analysis, future trials will be necessary to determine if efficacy of LTHT differs between patients with COPD and with bronchiectasis.

In summary, LTHT averaging 1–2 h/day resulted in significant improvements in exacerbation days, time to first exacerbation, lung function and QOL, in patients with COPD and bronchiectasis. The therapy was well tolerated, had no related adverse events, and the majority of patients opted to continue with the treatment at the conclusion of the 12-month trial period. Further studies, more disease specific, with longer daily treatment time by including overnight use, and physiological studies are recommended to confirm and extend our results and to gain insight into underlying mechanisms of LTHT in chronic airway disease.

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Conflict of interest statement

The Centre for Clinical Research and Effective Practice received funding from Fisher and Paykel Healthcare to conduct this clinical trial including financial support for the salaries of Professor Harry Rea, Associate Professor Jeff Garrett, and Dr Lata Jayaram. Professor Rea has received grants from Boehringer Ingelheim and The South Auckland Health Foundation. Matthew Payton is a Product Group Manager of Fisher and Paykel Healthcare and holds shares in Fisher and Paykel Healthcare Ltd. Kevin O'Donnell is a Product Manager of Fisher and Paykel Healthcare and holds shares in Fisher and Paykel Healthcare Ltd. Hans Hockey consults for Fisher and Paykel Healthcare Ltd.

Glenis O'Donnell holds shares in Fisher and Paykel Healthcare Ltd. Sue McAuley, Louanne Storey and Lynne Haru have no conflicts of interest to declare.

References

1. Bhowmik A, Seemungal TA, Sapsford RJ, Devalia JL, Wedzicha JA. Comparison of spontaneous and induced sputum for investigation of airway inflammation in chronic obstructive pulmonary disease. *Thorax* 1998 Nov;53(11):953–6.
2. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002 Oct;57(10):847–52.
3. Fuschillo S, De Felice A, Balzano G. Mucosal inflammation in idiopathic bronchiectasis: cellular and molecular mechanisms. *Eur Respir J* 2008 Feb;31(2):396–406.
4. Prescott E, Lange P, Vestbo J. Chronic mucus hypersecretion in COPD and death from pulmonary infection. *Eur Respir J* 1995 Aug;8(8):1333–8.
5. Rogers DF. Mucus pathophysiology in COPD: differences to asthma, and pharmacotherapy. *Monaldi Arch Chest Dis* 2000 Aug;55(4):324–32.
6. Martinez-Garcia MA, Perpina-Tordera M, Roman-Sanchez P, Soler-Cataluna JJ. Quality-of-life determinants in patients with clinically stable bronchiectasis. *Chest* 2005 Aug;128(2):739–45.
7. Wolkove N, Kamel H, Rotaple M, Baltzan Jr MA. Use of a mucus clearance device enhances the bronchodilator response in patients with stable COPD. *Chest* 2002 Mar;121(3):702–7.
8. Daviskas E, Anderson SD, Gomes K, Briffa P, Cochrane B, Chan K, et al. Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum. *Respirology* 2005;10(1):46–56.
9. Daviskas E, Anderson SD, Young IH, Lässig A, Charlton B. A placebo controlled trial with inhaled mannitol improves health related quality of life in patients with bronchiectasis. *Eur Respir J* 2004;24(Suppl. 48):707s.
10. Hasani A, Chapman TH, McCool D, Smith RE, Dilworth JP, Agnew JE. Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis. *Chron Respir Dis* 2008;5(2):81–6.
11. Mall MA, Harkema JR, Trojanek JB, Treis D, Livraghi A, Schubert S, et al. Development of chronic bronchitis and emphysema in {beta}-epithelial Na⁺ channel-overexpressing mice. *Am J Respir Crit Care Med* 2008 April;177(7):730–42.
12. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004 Jun;23:932–46.
13. Barker AF. Bronchiectasis. *N Engl J Med* 2002 May 2;346(18):1383–93.
14. Fletcher CMEP, Fairbairn MB, et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. *Br Med J* 1959;2:257–66.
15. Miller MR, Hankinson J, Brusasco V, Burgos D, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
16. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party standardization of lung function tests, European community for steel and coal. Official statement of the European respiratory society. *Eur Respir J Suppl* 1993 Mar;16:5–40.
17. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002 Jul;166(1):111–7.
18. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's respiratory questionnaire. *Am Rev Respir Dis* 1992 Jun;145(6):1321–7.

19. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002 Mar; **19**(3):398–404.
20. Efthimiadis A, Spanevello A, Hamid Q, Kelly MM, Linden M, Louis R, et al. Methods of sputum processing for cell counts, immunocytochemistry and in situ hybridisation. *Eur Respir J Suppl* 2002 Sep; **37**:19s–23s.
21. Burge S, Wedzicha JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl* 2003 Jun; **41**:46s–53s.
22. Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Aust Crit Care* 2007 Nov; **20**(4):126–31.
23. Brack T, Senn O, Russi EW, Bloch KE. Transtracheal high-flow insufflation supports spontaneous respiration in chronic respiratory failure. *Chest* 2005 Jan; **127**(1):98–104.
24. Aaron SD, Fergusson D, Marks GB, Suissa S, Vandemheen KL, Doucette S, et al. Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. *Thorax* 2008 Feb; **63**(2):122–8.
25. Jones P, Higenbottam T. Quantifying of severity of exacerbations in chronic obstructive pulmonary disease: adaptations to the definition to allow quantification. *Proc Am Thorac Soc* 2007; **4**(8):597–601.
26. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007 April; **146**(8):545–55.
27. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; **356**(8):775–89.
28. Dysart K, Miller TL, Wolfson MR, Shaffer TH. Research in high flow therapy: mechanisms of action. *Respir Med* 2009; **103**(10):1400–5.
29. Tsolaki V, Pastaka C, Karetsi E, Zygoulis P, Koutsokera A, Gourgoulisian KI, et al. One-year non-invasive ventilation in chronic hypercapnic COPD: effect on quality of life. *Respir Med* 2008 Jun; **102**(6):904–11.
30. O'Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. *Thorax* 2000 Aug; **55**(8):635–42.