Long-term benefits of airway clearance in bronchiectasis: a randomised placebo-controlled trial

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ABSTRACT Keeping airways clear of mucus by airway clearance techniques seems essential in bronchiectasis treatment, although no placebo-controlled trials or any studies lasting longer than 3 months have been conducted. We evaluate the efficacy of the ELTGOL (slow expiration with the glottis opened in the lateral posture) technique over a 1-year period in bronchiectasis patients with chronic expectoration in a randomised placebo-controlled trial.

Patients were randomised to perform the ELTGOL technique (n=22) or placebo exercises (n=22) twice-daily (ClinicalTrials.gov, NCT01578681). The primary outcome was sputum volume during the first intervention and 24 h later. Secondary outcomes included sputum volume during the intervention and 24 h later at month 12, exacerbations, quality of life, sputum analyses, pulmonary function, exercise capacity, systemic inflammation, treatment adherence, and side effects.

Sputum volume during intervention and 24 h later was higher in the ELTGOL group than in the placebo group both at the beginning and end of the study. Patients in the ELTGOL group had fewer exacerbations ($p=0.042$) and a clinically significant improvement in the St George's Respiratory Questionnaire score ($p<0.001$) and the Leicester Cough Questionnaire score compared with the placebo group ($p<0.001$).

Twice-daily ELTGOL technique over 1 year in bronchiectasis patients facilitated secretion removal and was associated with fewer exacerbations, improved quality of life, and reduced cough impact.

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Conflict of interest: None declared.

Introduction

Bronchiectasis is a chronic lung disorder with impaired mucociliary clearance, mainly in the peripheral airways, that causes mucus retention and leads to chronic bronchial infection and inflammation. Removing secretions by airway clearance techniques (ACTs) has been recommended in those patients with chronic productive cough [1], mucus plugging on chest computed tomography (CT) [2, 3], and in all patients with cystic fibrosis (CF) [4], despite there being little scientific evidence regarding its benefits [5, 6]. ACTs are expected to modify the viscoelastic properties of secretions, increase gas–liquid interactions and facilitate secretion removal. These effects are based on changes in pulmonary volumes, pressures and expiratory flows, the effect of gravity, or the application of compressive or vibratory forces, depending on the technique used [3]. Few short-term controlled trials in adults with bronchiectasis with different ACTs have been published [7–11], and there is no evidence regarding which technique is the most effective. The longest study was a 3-month crossover trial in 20 patients where a twice-daily Acapella device improved perceived cough severity, quality of life and exercise capacity, and increased 24-h sputum volume, compared with no physiotherapy [9].

Slow expiration with the glottis opened in the lateral posture (ELTGOL) [12] is an ACT whose effect is based on increasing airflow resistance and air flow–mucus interaction [13] by reducing the diameter of the peripheral airways of the inferolateral lung. This reduction in diameter results from the weight of the superolateral lung and mediastine, from inferolateral hemidiaphragm displacement in a cephalad direction due to compression of the viscera, and from slow and prolonged expiration, which confers the added benefit of avoiding airway collapse [12, 13]. On studying the ELTGOL efficacy in a single session in 15 patients with CF and 10 patients with bronchiectasis, it was found that secretion removal was greater than that obtained with Flutter [7, 14]. In a recent crossover study, three non-consecutive ELTGOL sessions over a 1-week period in 31 patients with bronchiectasis achieved a similar level of sputum expectoration (during the sessions) to that obtained with autogenic drainage, and greater expectoration than with temporary positive expiratory pressure. Of the total daily sputum, 42.3% was expectorated during the ELTGOL session; however, the overall sputum clearance was similar to baseline [8].

No placebo-controlled trials with an ACT in bronchiectasis or any studies lasting longer than 3 months have been reported to date. Therefore, a randomised placebo-controlled study was conducted to evaluate the efficacy of twice-daily ELTGOL technique, in patients with bronchiectasis and daily productive cough, over a 1-year period.

Methods

Study design

The study comprised a 12-month randomised placebo-controlled trial of twice-daily ELTGOL technique in bronchiectasis patients. The study was conducted at the Dr Josep Trueta University Hospital and the Vall d'Hebron Hospital with the same respiratory physiotherapist and following the same care criteria [1], and was approved by the ethical committees of the two centres (registration numbers: 082010 and PR(AG)194/2013, respectively). All patients provided written informed consent (ClinicalTrials.gov NCT01578681).

Study population

The study population comprised adult patients with bronchiectasis confirmed *via* chest CT images observed at the two centres, in stable state (no exacerbations in the previous month), with chronic sputum of 10 mL or more daily over the previous year, who were not practising any regular ACT or pulmonary rehabilitation.

Exclusion criteria were CF, current smokers or a smoking history of more than a 10 pack-year, following any mucoactive treatment, knowledge of any effective ACT for the peripheral airways, inability to perform ACT or to attend the visits, and any contraindication for physiotherapy.

Randomisation and masking

Patients were randomly assigned to either perform ELTGOL or placebo (1:1) and were blinded to which group they belonged to. Computer-generated randomisation was performed at baseline without stratification. The chest physicians and the statistician were masked to the technique assignment throughout the study.

Procedures

The ELTGOL technique [12] consists of performing slow and prolonged expirations with the glottis opened, from the functional residual capacity to the residual volume, in the lateral decubitus position with the affected lung in the inferolateral position. In addition, during the expiration, chest and abdominal compressions were performed by the patients to enhance the technique's efficacy [15]. Placebo exercises

consisted of repeated sequences of upper-limb stretching exercises, involving the brachial biceps, triceps, deltoids, pectoralis major and latissimus dorsi. Patients were trained by the physiotherapist and required to perform either the ELTGOL or the placebo exercises twice-daily for 15 min in patients with only one lung affected, and 30 min when both lungs were affected (15 min each side in the ELTGOL group).

Any change to the patients' usual respiratory medication was to be avoided during the study period and noted down if found to be necessary. An exacerbation was defined as an acute development and persistence of changes in sputum characteristics (increased volume, thicker consistency, greater purulence, or haemoptysis), and/or increased breathlessness unrelated to other causes [1]. All patients who experienced an exacerbation during the study were assessed by the study's chest physicians. The interventions continued during exacerbations.

Assessments

All patients were assessed at seven visits: at baseline entry to the study, 24 h later at visit 2 (randomisation, instruction for performing the intervention) and at months 1, 3, 6, 9 and 12. The assessments conducted are described below.

Sputum analysis

Patients were given a calibrated container at the baseline visit and instructed to collect all the sputum expectorated in the subsequent 24 h. Each patient was also provided with a container at each subsequent visit to collect a fresh and spontaneously expectorated sample at any point during the visit for a qualitative culture and for the recording of the sputum colour [16]. The sputum samples obtained during the intervention performed in the hospital at visit 2, month 6 and month 12 were measured. Another calibrated container was supplied to the patients for the collection of all the sputum expectorated in the 24 h after the intervention performed at the hospital at visit 2, month 6 and month 12.

Quality of life

The St George's Respiratory Questionnaire (SGRQ) [17], the Leicester Cough Questionnaire (LCQ) [18] and the modified Medical Research Council (mMRC) dyspnoea scale [19] were completed at baseline, month 6 and month 12. The SGRQ is a 50-item self-administered quality-of-life measure of the impact of respiratory symptoms, validated for use in bronchiectasis. The total score ranges from 0 to 100; a higher score indicates a poorer health-related quality of life. The minimum clinically important difference (MCID) is 4 units [20]. The LCQ is a 19-item self-completed quality-of-life measure of chronic cough, validated for use in bronchiectasis. The total severity score ranges from 3 to 21, with a lower score indicating a more severe cough. The MCID for change is 1.3 units [21].

Spirometry

Spirometry [22] was performed at baseline, month 6 and month 12, and the 6-min walk test at baseline and month 12 according to standardised guidelines [23].

Systemic inflammation

Venous blood was collected at baseline and month 12 for total leukocyte and neutrophil count, C-reactive protein, erythrocyte sedimentation rate, and fibrinogen.

Physiotherapist review

At each visit the physiotherapist reviewed the intervention technique and the diary card recording compliance. Good adherence was considered if 80% or more of the sessions were performed [24].

Side effects

Any complications and arterial oxygen saturation in ambient air during the intervention (with a pulse oximeter Pulsox-300i; Konica Minolta, Newark, NJ, USA), and Borg scale [25] at the end of the intervention, were recorded at visit 2, month 6 and month 12.

All treatments and assessments were undertaken by the chest physician of each centre except for the following actions, which were carried out by the physiotherapist: the performance of the intervention itself, the recording of the side effects and compliance, and the collection of the sputum volume during the intervention.

Outcomes

The primary outcome was sputum volume in millilitres during the first intervention and 24 h later. Secondary outcomes included sputum volume during the intervention and 24 h later at month 12, frequency of exacerbations and the time to the first exacerbation, the LCQ and SGRQ scores, purulence of

sputum, qualitative sputum bacteriology, the mMRC dyspnoea scale score, forced expiratory volume in 1 s (FEV_1), exercise capacity, systemic inflammation, treatment adherence and side effects.

Statistical analysis

A sample size of 17 in each group would be required to have 80% power to detect a minimal difference of 15 mL in the 24-h sputum volume, assuming that the common standard deviation was 15 mL (data obtained from an internal database [26] as no previous studies in bronchiectasis using this variable as a primary outcome were available), using a two-group t-test with a 0.05 two-sided significance level (nQuery Advisor, Los Angeles, CA, USA). These values of minimal difference and standard deviation will permit the detection of a high effect size equal to, or greater than, 1.

Descriptive statistics are provided for subgroup comparisons, including absolute and relative frequencies (n, %) for categorical variables and mean±SD or median (quartiles) for quantitative variables depending on the normality of the distribution. Normal distribution was assessed with normal Q-Q plots, the Kolmogorov–Smirnov test and the Shapiro–Wilk test. The quality-of-life results were expressed as the difference between month 6 and baseline and between month 6 and month 12, and a comparison is made between the ELTGOL and placebo groups. 24-h sputum volume, quality of life, pulmonary function, dyspnoea scale, exercise capacity and inflammatory markers were expressed, comparing pre- and post-treatment differences between the two groups (ELTGOL *versus* placebo). Variables were compared using the unpaired t-test for normally distributed parameters and the Mann–Whitney U-test for non-normally distributed parameters. Differences between variables were expressed as mean or median (95% CI) depending on their distribution. To evaluate the effect of the treatment over the whole period of the study, we fit a linear mixed model where treatment, time and baseline 24-h sputum volume were considered as fixed effects and intercept was considered as random effects; if the 24-h sputum volume was not normally distributed, we would apply a Box-Cox transformation to achieve normal distribution. A p-value of <0.05 was considered significant. Statistical analyses were performed using SPSS 23.0 and R software (R Development Core Team, 2010).

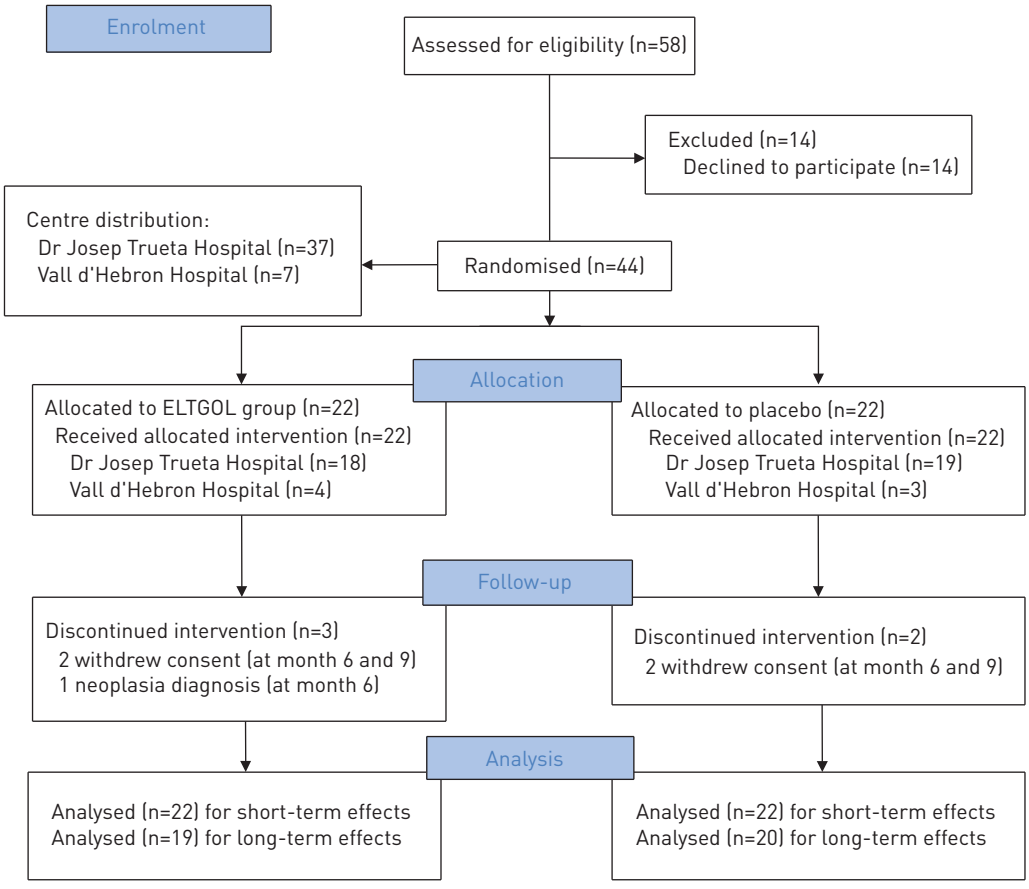

FIGURE 1 Trial profile.

TABLE 1 Baseline characteristics of the patients

	ELTGOL group (n=22)	Placebo group (n=22)	p-value
Sex			0.365
Males	12 (55.5)	9 (40.9)	
Females	10 (45.5)	13 (59.1)	
Age years	63.1±13.5	66.8±8.4	0.272
Ex-smokers	7 (31.8)	9 (40.9)	0.531
BMI kg·m^{-2}	24.3±3.5	25.7±4.2	0.238
Exacerbations in the past year[¶]	2 (1–3.25)	1 (0.75–2.25)	0.189
Aetiology[#]			0.368
Post-infective	9 (40.9)	4 (18.2)	
Idiopathic	7 (31.8)	10 (45.5)	
Immune deficiency	2 (9.1)	1 (4.5)	
Gastro-oesophageal reflux	2 (9.1)	5 (22.7)	
Other	2 (9.1)	2 (9.1)	
24-h sputum volume mL	20 (15–40)	15 (15–20)	0.061
Sputum colour[#]			0.074
Mucous	2 (9.1)	7 (31.8)	
Mucopurulent	13 (59.1)	13 (59.1)	
Purulent	7 (31.8)	2 (9.1)	
Quality sputum culture			0.093
No bacterial growth	7 (31.8)	9 (40.9)	
Pseudomonas aeruginosa	6 (27.3)	2 (9.1)	
Haemophilus influenzae	4 (18.2)	1 (4.5)	
Other PPMs	3 (13.6)	5 (22.7)	
No sample collected	2 (9.1)	5 (22.7)	
FEV$_1$% predicted	58.1±22.9	64.6±21.1	0.336
FEV$_1$ L	1.6±0.8	1.5±0.4	0.762
Number of affected lobes[#]			0.469
1	0 (0)	3 (13.6)	
2	10 (45.5)	7 (31.8)	
3	2 (9.1)	3 (13.6)	
4	7 (31.8)	7 (31.8)	
⩾5	3 (13.6)	2 (9.1)	
SGRQ score units	40.2±13.7	35.0±9.9	0.157
LCQ score units	14.5±3.4	15.7±1.9	0.160
mMRC[¶]	1 (0–1.25)	1 (1–1.25)	0.511
6MWT m	417.8±67	382.9±76.9	0.116
BSI[#]			0.090
Mild	2 (9.1)	8 (36.4)	
Moderate	10 (45.5)	6 (27.3)	
Severe	10 (45.5)	8 (36.4)	
FACED score[#]			0.640
Mild	11 (50)	14 (63.6)	
Moderate	9 (40.9)	7 (31.8)	
Severe	2 (9.1)	1 (4.5)	
Long-term antibiotic therapy[#]			0.408
Inhaled antibiotic	8 (36)	6 (27)	
Oral antibiotic	4 (18)	2 (9)	
Oral corticosteroid therapy[#]	1 (4.5)	2 (9.1)	1
Inhaled corticosteroid therapy	16 (72.7)	17 (77.3)	0.728
Inhaled bronchodilator therapy	16 (72.7)	18 (81.8)	0.360

Data are presented as n (%), median (interquartile range) or mean±SD. [#]: Fisher's test; [¶]: Mann–Whitney U-test. BMI: body mass index; PPMs: potentially pathogenic microorganisms (*S. pneumoniae, S. aureus, Enterobacter, Klebsiella, Proteus*); FEV$_1$: forced expiratory volume in 1 s; SGRQ: St George's Respiratory Questionnaire; LCQ: Leicester Cough Questionnaire; mMRC: modified Medical Research Council dyspnoea scale; 6MWT: 6-min walk test; BSI: bronchiectasis score index.

Results

A total of 58 patients were screened for eligibility from September 2011 to June 2015, and of these, 44 were randomised (ELTGOL, n=22; placebo, n=22)—four with unilateral bronchiectasis and 40 (91%) with

bilateral bronchiectasis—and performed 15- and 30-min interventions, respectively. Three patients in the ELTGOL group and two patients in the placebo group did not complete the study (figure 1). Baseline characteristics are shown in table 1. No significant differences were found between the groups. No changes were made to any patient's routine respiratory treatment during the study.

The sputum volume obtained while performing ELTGOL at the first intervention was 12.27±11.93 mL, including two patients who did not cough up sputum during the procedure, whereas no sputum at all was obtained from any patient in the placebo group for the duration of their exercise. The 24-h sputum volume after this intervention was higher in the ELTGOL group than in the placebo group (p<0.001), taking into account that a second intervention was performed at home. The sputum volume obtained while performing ELTGOL at month 12 was 10.83±5.21 mL, including one patient who did not cough up sputum, whereas no sputum at all was obtained from any patient in the placebo group for the duration of their exercise. The 24-h sputum volume after this intervention was also higher in the ELTGOL group than in the placebo group (p=0.001). The overall 24-h sputum volume in the ELTGOL group was higher than baseline at both visit 2 and month 12 (p=0.001 and p=0.026, respectively). After 1 year of performing twice-daily ELTGOL, the overall 24-h sputum volume was lower than at visit 2, although the difference was not significant (table 2).

The linear mixed model showed that the mean difference (95% CI) of the overall 24-h sputum volume (during intervention and 24 h later) was higher for the ELTGOL group at all times, calculated thus: ELTGOL *versus* placebo at visit 2: 16.96 mL (9.63–25.70 mL); ELTGOL *versus* placebo at month 6: 18.24 mL (10.46–27.45 mL); and ELTGOL *versus* placebo at month 12: 17.10 mL (9.72–25.90 mL).

There were fewer exacerbations during the 12-month period in the ELTGOL group than in the placebo group (p=0.042) (table 3). Thirteen patients in the ELTGOL group and 16 in the placebo group had an exacerbation during the study. The time to the first exacerbation was 226 (40.25–298.50) days in the ELTGOL group and 85 (54–161) days in the placebo group (p=0.131). The ELTGOL group showed a clinically significant improvement in both the SGRQ total score (−7.69±8.61) and the LCQ total score (1.89±4.03) compared with the placebo group at 6 months, and these changes still held at the end of the study. Analysis of the three domains of the SGRQ also showed a clinically significant improvement in the ELTGOL group compared to the placebo group (table 4). No differences in the mMRC scale, FEV_1, exercise capacity, systemic inflammatory markers, or the sputum analysis between baseline and the end of the study were observed (tables 3 and 5).

An adherence of 80% or more was recorded in all patients in the ELTGOL group and in 15 (75%) in the placebo group (p=0.047). Minor corrections to the performance of the ELTGOL technique were required in five patients during the study (23%). No adverse effects appeared in either group during the study.

Discussion

The present study is the first long-term randomised controlled trial of an ACT and the first to compare an ACT with a placebo in patients with bronchiectasis. Performance of the ELTGOL technique twice-daily

TABLE 2 Sputum volume obtained during the study

	Sputum volume mL		p-value
	ELTGOL group	Placebo group	
Baseline 24-h	20 (15–40)	15 (15–20)	0.061
Visit 2 overall 24-h	40 (23.75–60)	12.5 (0–20)	<0.001
During intervention	12.27±11.93	0	
24 h later	30 (20–45)	12.5 (0–20)	<0.001
Difference between visit 2 and baseline[+]	17.5 (10–26.25)	−5 (−11.25–0)	<0.001
Month 12 overall 24-h	35 (30–50)	15 (10–20)	<0.001
During intervention	10.83±5.21	0	
24 h later	25 (20–40)	15 (10–20)	0.001
Difference between month 12 and baseline[#]	10 (−5–25)	0 (−10–3.75)	0.015
Difference between month 12 and visit 2[¶]	−5 (−30–5)	5 (5–10)	0.019

Data are presented as mean±SD and median (interquartile range); differences are expressed as median (95% confidence interval). Unpaired t-test values of the differences in the overall 24-h sputum volume between visit 2 and baseline[+], month 12 and baseline[#], month 12 and visit 2[¶] in the ELTGOL group (p=0.001, p=0.026, p=0.09, respectively) and in the placebo group (p=0.008, p=0.106, p=0.261, respectively).

TABLE 3 Quality of life, pulmonary function, dyspnoea scale, exercise capacity and inflammatory markers between the groups at the beginning and the end of the study

	ELTGOL			Placebo			p-value[#]
	Baseline	Month 12	Between-group differences	Baseline	Month 12	Between-group differences	
SGRQ total score	40.2±13.7	33.7±15.7	−6.8 (−15.1–1.5)[+]	35.0±9.9	47.6±12.8	11.4 (6.9–15.9)[+]	<0.001
LCQ total score	14.5±3.4	16.2±3.2	1.96 (0.2–3.8)[+]	15.7±2	13.7±2.1	−2 (−2.8– −1.2)[+]	<0.001
Exacerbations	2 (1–3.25)	1 (0–2)	−0.8 (−1.5– −0.1)[¶]	1(0.75–2.25)	2 (1–3)	0.35 (−0.5–0.35)[¶]	0.042
FEV_1% predicted	58.1±22.9	57.9±25	−0.4 (−3.5–2.8)[+]	64.6±21.1	61.3±21	−2.5 (−4.7– −0.2)[+]	0.262
FEV_1 L	1.6±0.8	1.6±0.8	−0.004 (−0.1–0.03)[+]	1.5±0.4	1.5±0.4	−0.1 (−0.2–0.004)[+]	0.407
mMRC	1 (0–1.25)	1 (0–1)	0 (−0.5–0)[¶]	1 (1–1.25)	1 (1–2)	0.5 (0–0.5)[¶]	0.127
6MWT m	417.8±67	423.5±84.9	2.3 (−16.7–21.2)[+]	382.9±76.9	377.8±57.3	−2.6 (−29.3–24.1)[+]	0.746
ESR mm	22.3±26.5	17.1±17.5	9 (7–23)[+]	25.5±22.3	23.9±17.6	24 (7.3–34.5)[+]	0.863
Leukocytes $\times 10^3$ μL^{-1}	6.9±2	7.5±2	0.03 (−0.8–0.9)[+]	7.5±2.2	7.7±2.7	0.6 (−0.2–1.3)[+]	0.641
Neutrophils %	59.7±8.7	60±8.9	−1.6 (−6.6–3.3)[+]	58.5±8.4	57.9±12.1	−1.4 (−6–3.2)[+]	0.945
CRP mg·dL^{-1}	0.7±0.9	1.7±2.7	0.7 (−0.7–2.2)[+]	0.6±0.5	0.7±0.6	0.06 (−0.3–0.4)[+]	0.619
Fibrinogen mg·dL^{-1}	425.5±69	468.6±1000.5	43.9 (−31.3–119)[+]	449.6±930.5	492.6±125.2	59.3 (−13.8–132.3)[+]	0.756

Data are presented as median (interquartile range) or mean±SD, unless otherwise stated. [#]: unpaired t-test comparing difference between baseline and month 12 between the two groups (ELTGOL *versus* placebo); [¶]: data are presented as median difference (95% confidence interval); [+]: data are presented as mean difference (95% confidence interval). SGRQ: St George's Respiratory Questionnaire; LCQ: Leicester Cough Questionnaire; FEV_1: forced expiratory volume in 1 s; mMRC: modified Medical Research Council; 6MWT: 6-min walk test; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

over a 1-year period increased the 24-h sputum volume from the very first day, and this was associated with fewer exacerbations, an improvement in quality of life, and a reduction in the impact of coughing.

Antibiotic treatment and the removal of purulence are essential elements in the treatment of any infection. Furthermore, in patients with bronchiectasis it is important to maintain the airways such that they are as clear from mucus as possible in order not to provide favourable conditions for bronchial colonisation [27]. We selected the ELTGOL technique owing to its effect on the clearance of the peripheral airways [12, 13], which is where bronchiectasis is commonly located, and because it can be self-administered [15] it is easier to learn than ACTs such as autogenic drainage, and does not require the use of devices. After the technique has been carefully taught to the patient through practice, it is only necessary for this to be followed up periodically by a respiratory physiotherapist to ensure that good performance is being maintained. In this study the adherence and quality of the performance of ELTGOL were good, and no secondary effects were observed.

Sputum was obtained during the first ELTGOL technique session but not during the placebo exercises, which indicates that, unlike the placebo, the technique has an effect in clearing secretions. Comparison of the sputum obtained during a single ELTGOL session with the two previous studies is difficult because of the different measures used (dry [7] or wet [8] sputum weight). In these other studies, the sputum obtained during ELTGOL was similar to that obtained during autogenic drainage, and greater than during temporary positive expiratory pressure [8], during Flutter, and in a control group without any intervention [7]. The present study is the first to attempt the use of a placebo (stretching exercises) with a manual ACT. These exercises were chosen as a placebo, given that, firstly, they would not have any effect on airway clearance, and secondly, training was required. Whereas it would have been ideal to use a sham as this would facilitate blinding, this is difficult to do when no device is being used. Figueiredo *et al.* [10] compared the short-term effects of Flutter to a sham flutter intervention. They obtained higher sputum removal during Flutter; however, the sputum obtained during the sham flutter was 19.6±3.6 mL, a higher volume than that obtained in our study during ELTGOL. Although baseline sputum was higher than in our study, the sham used here should not be considered as a true placebo as starting the breathing through the device at full pulmonary capacity probably affected secretion clearance. In the present study the 24-h sputum volume obtained after the first intervention was higher in the ELTGOL group, taking into account that a second intervention was performed at home, and so the overall 24-h sputum volume was higher than at baseline. This suggests that twice-daily ELTGOL is more effective than once daily, where sputum volume has been found to be similar to baseline [8].

After 1 year performing ELTGOL, the overall sputum volume continued to be higher than placebo and a median of 10 mL higher than at baseline. Furthermore, this was associated with fewer exacerbations, an improvement in quality of life, and reduced cough impact. In the longest study published to date of an

TABLE 4 Changes in the St George's Respiratory Questionnaire (SGRQ) and the Leicester Cough Questionnaire (LCQ) in the two groups over the study period

	Month 6 – visit 2				Month 12 – month 6			
	ELTGOL[#]	Placebo[#]	Mean difference (95% CI)[¶]	p-value[+]	ELTGOL[#]	Placebo[#]	Mean difference (95% CI)[¶]	p-value[+]
SGRQ total	−7.7±8.6	7.8±10.5	−15.51 (−22.10; −8.92)	<0.001	0.8±14	1.6±9.6	−0.78 (−9.07; 7.50)	0.848
SGRQ symptoms	−8.3±21.4	6.2±10.3	−14.50 (−26.11; −2.89)	0.017	−1±17.9	0.7±15.8	−1.65 (−9.04; 9.54)	0.775
SGRQ activity	−4.5±12	8.6±14.5	−13.06 (−22.17; −3.95)	0.006	0.4±14.4	2.5±15.8	−2.10 (−12.46; 8.26)	0.683
SGRQ impact	−9.3±10.5	7.9±13.2	−17.23 (−25.40; −9.06)	<0.001	1.6±16.4	1.4±9.5	0.25 (−9.04; 9.54)	0.957
LCQ total	1.9±4	−1.6±2.6	3.53 (1.20; 5.86)	0.004	0.002±3.5	−0.5±2.2	0.48 (−1.54; 2.50)	0.633

[#]: values represent mean difference and standard deviations in score questionnaire between month 6 and visit 2 and between month 6 and month 12; [¶]: values represent mean differences in the variable "difference in score questionnaire between month 6 and visit 2" and "difference in score questionnaire between month 12 and month 6" between groups (ELTGOL *versus* placebo) and their 95% confidence interval; [+]: unpaired t-test.

ACT, the median increase in the 24-h sputum volume using the Acapella device twice-daily over a 3-month period was 2 mL, although the median 24-h volume at baseline was lower than in our study [9]. Shorter studies with other ACTs [9] or with the ELTGOL technique in chronic obstructive pulmonary disease [28] have not been able to confirm a reduction in the number of exacerbations, one of the main objectives in the management of bronchiectasis given that exacerbations are associated with morbidity and a lower quality of life [17].

A significant improvement in quality of life and cough impact were observed following 6 months of treatment with ELTGOL, and this was maintained up to the end of the 12-month period of the study. The reduction in the SGRQ in both the total score and each of the three domains (symptoms, activity and impact) was higher than the MCID of 4 units [20]. The significant improvement in patients' perception of cough severity measured by the LCQ, a common symptom probably related to mucus in the airways, was also higher than the MCID of 1.3 units [21].

These results are consistent with the previous 3-month study with Acapella [9], although the only significant improvement reported in the individual domains of the SGRQ score in that study was in the activity domain, which is the domain that is most related to dyspnoea and the limitation of daily life activities and that which is least related to the expected effects of ACTs.

Unlike Murray *et al.* [9], we did not observe any improvement in exercise capacity. Comparison of the two studies is difficult as different measurement instruments were used (Murray *et al.* [9] used the shuttle test whereas we used the 6-min walk test) and their study population was older and had better pulmonary function. It will probably be necessary to combine an ACT with a specific muscular training programme in order to improve exercise capacity, given that the main effect of ACT is to facilitate the removal of secretions [29]. We observed no changes in FEV_1, and 1 year is probably insufficient to appreciate differences in the progression of this disease, as has been observed in other studies in these patients [9, 30–32].

Some limitations to this study should be mentioned. Firstly, although we have strong reasons to believe that the impossibility of blinding the physiotherapist as to whether or not the patient was practising the

TABLE 5 Qualitative sputum bacteriology throughout the study

	ELTGOL group (n=22)			Placebo group (n=22)		
Microorganism	**Baseline**	**Month 6**	**Month 12**	**Baseline**	**Month 6**	**Month 12**
Pseudomonas aeruginosa	6 (27.3)	7 (36.8)	5 (26.3)	2 (9.1)	2 (10.0)	4 (20.0)
Haemophilus influenzae	4 (18.2)	4 (18.2)	2 (10.5)	1 (4.5)	3 (15.0)	3 (15.0)
Other PPMs	3 (13.6)	1 (5.3)	3 (15.8)	5 (22.7)	4 (20.0)	2 (10.0)
MNF or no bacterial growth	7 (31.8)	4 (21.1)	9 (47.4)	9 (40.9)	4 (20.0)	8 (40.0)
No sample collected	2 (9.1)	3 (15.3)	0 (0.0)	5 (22.7)	7 (35.0)	3 (15.0)

Data are presented as n (%). PPMs: potentially pathogenic microorganisms (*S. pneumoniae*, *S. aureus*, *Enterobacter*, *Klebsiella*, *Proteus*); MNF: mixed normal flora.

ELTGOL technique or placebo exercises was not a limiting factor, it is important to report this possibility, which must necessarily exist in all ACT studies. Secondly, we cannot be completely sure that patients were effectively blinded. However, knowledge of effective ACTs for peripheral airway clearance was an exclusion criterion, although nobody was excluded for this reason as little was known about ACTs in general in the geographical area of our study, as we demonstrated in a preliminary study [33]. Thirdly, the accuracy of adherence findings is dependent on the patient's own reporting, although mid-study revisions by the physiotherapist and the objective benefits observed strongly support good adherence. Fourthly, it is not possible to be sure that participants in the study collected all of the sputum produced over the 24-h period, although this is a problem that is equally applicable to both groups. Finally, whereas recruitment difficulties did not allow us to meet our initial patient inclusion target, it should be noted that our primary end-point was achieved and that this study managed to enrol more patients than any previous bronchiectasis ACT trial. The strengths of this trial include the lengthy period over which the study was performed, the homogeneity of the patients' management at the two hospitals, and the fact that the interventions were performed by the same physiotherapist.

Despite no significant differences being found between the two groups at baseline, the ELTGOL group had a 24-h median sputum volume that was 5 mL greater, had more patients in the group with purulent sputum and isolation of *Pseudomonas aeruginosa*, and had more severe bronchiectasis, as measured by two scores predicting long-term mortality. It is reasonable to assume that the benefits of ELTGOL will probably be greater in those patients with more secretions in the lower airways and those with more exacerbations. However, more patients in the ELTGOL group were on long-term antibiotic therapy, which could interfere with the positive effect of the physiotherapy. Ultimately, though, the differences at baseline between the two groups are too small to allow firm conclusions to be drawn.

In conclusion, twice-daily ELTGOL technique over 1 year in bronchiectasis patients facilitated secretion removal and was associated with fewer exacerbations, improvement in quality of life, and reduced cough impact. Given the low adherence to ACTs in clinical practice, these findings may help to generalise their use. We postulate, in accordance with previous studies using other treatments, that 3–6 months will probably be sufficient to detect changes in the quality of life in these patients [9, 30, 31, 32]; however, longer treatment periods are necessary to evaluate the effect on exacerbations [9, 30].

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References

1 Vendrell M, de Gracia J, Olveira C, *et al.* Diagnosis and treatment of bronchiectasis. Spanish Society of Pneumology and Thoracic Surgery. *Arch Bronconeumol* 2008; 44: 629–640.
2 Pasteur MC, Bilton D, Hill AT. British Thoracic Society Non-CF Bronchiectasis Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010; 65: Suppl. 1, i1–58.
3 Bott J, Blumenthal S, Buxton M, *et al.* Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. *Thorax* 2009; 64: Suppl. 1, i1–51.
4 Flume PA, Robinson KA, O'Sullivan BP, *et al.* Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care* 2009; 54: 522–537.
5 Lee AL, Burge A, Holland AE. Airway clearance techniques for bronchiectasis. *Cochrane Database Syst Rev* 2015; CD008351.
6 Warnock L, Gates A. Chest physiotherapy compared to no chest physiotherapy for cystic fibrosis. *Cochrane Database Syst Rev* 2015; CD001401.
7 Guimarães FS, Moço VJ, Menezes SL, *et al.* Effects of ELTGOL and Flutter VRP1® on the dynamic and static pulmonary volumes and on the secretion clearance of patients with bronchiectasis. *Rev Bras Fisioter* 2012; 16: 108–113.
8 Herrero-Cortina B, Vilaró J, Martí D, *et al.* Short-term effects of three slow expiratory airway clearance techniques in patients with bronchiectasis: a randomised crossover trial. *Physiotherapy* 2016; 102: 357–364.
9 Murray MP, Pentland JL, Hill AT. A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009; 34: 1086–1092.
10 Figueiredo PH, Zin WA, Guimarães FS. Flutter valve improves respiratory mechanics and sputum production in patients with bronchiectasis. *Physiother Res Int* 2012; 17: 12–20.
11 Nicolini A, Cardini F, Landucci N, *et al.* Effectiveness of treatment with high-frequency chest wall oscillation in patients with bronchiectasis. *BMC Pulm Med* 2013; 13: 1–8.
12 Postiaux G, Lens E, Alsteens G, *et al.* Efficacité de l'expiration lente totale glotte ouverte en décubitus láteral (ELTGOL): sur la toilette en périphérie de l'arbre trachéobronchique. *Ann Kinésithér* 1990; 17: 87–99.

13 Martins JA, Dornelas de Andrade A, Britto RR, *et al.* Effect of slow expiration with glottis opened in lateral posture (ELTGOL) on mucus clearance in stable patients with chronic bronchitis. *Respir Care* 2012; 57: 420–426.
14 Guimarães FS, Lopes AJ, Moço VJ, *et al.* Eltgol acutely improves airway clearance and reduces static pulmonary volumes in adult cystic fibrosis patients. *J Phys Ther Sci* 2014; 26: 813–816.
15 Lanza FC, Alves CS, dos Santos RL, *et al.* Expiratory reserve volume during slow expiration with glottis opened in infralateral decubitus position (ELTGOL) in chronic pulmonary disease: technique description and reproducibility. *Respir Care* 2015; 60: 406–411.
16 Murray MP, Pentland JL, Turnbull K, *et al.* Sputum colour: a useful clinical tool in non-cystic fibrosis bronchiectasis. *Eur Respir J* 2009; 34: 361–364.
17 Wilson CB, Paul WJ, O'Leary CJ, *et al.* Validation of the St. George's respiratory questionnaire in bronchiectasis. *Am J Respir Crit Care Med* 1997; 156: 536–541.
18 Muñoz G, Buxó M, de Gracia J, *et al.* Validation of a Spanish version of the Leicester cough questionnaire in non-cystic fibrosis bronchiectasis. *Chron Respir Dis* 2016; 13: 128–136.
19 Brooks SM. Surveillance for respiratory hazards. *ATS News* 1982; 8: 12–16.
20 Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; 19: 398–404.
21 Raj AA, Pavord DI, Birring SS. Clinical cough IV: what is the minimal important difference for the Leicester cough questionnaire? *Handb Exp Pharmacol* 2009; 187: 311–320.
22 Roca J, Sanchís J, Agustí-Vidal A, *et al.* Spirometric reference values from a Mediterranean population. *Bull Eur Physiopathol Respir* 1986; 22: 217–224.
23 ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002; 166: 111–117.
24 Hansen RA, Kim MM, Song L, *et al.* Comparison of methods to assess medication adherence and classify non adherence. *Ann Pharmacother* 2009; 43: 413–422.
25 Borg GAV. Psychophysical basis of perceived exertion. *Med Sci Sports Exerc* 1982; 14: 377–381.
26 Vendrell M, Fernández P, de Gracia J, *et al.* Alterations to innate immunity in patients with bronchiectasis. *Eur Respir J* 2013; 42: Suppl. 57, PA4648.
27 Currie DC, Pavia D, Agnew JE, *et al.* Impaired tracheobronchial clearance in bronchiectasis. *Thorax* 1987; 42: 126–130.
28 Kodric M, Garuti G, Colomban M, *et al.* The effectiveness of a bronchial drainage technique (ELTGOL) in COPD exacerbations. *Respirology* 2009; 14: 424–428.
29 Mandal P, Sidhu MK, Kope L, *et al.* A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis. *Respir Med* 2012; 106: 1647–1654.
30 Murray MP, Govan JR, Doherty CJ, *et al.* A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. *Am J Respir Crit Care Med* 2011; 183: 491–499.
31 Haworth CS, Foweraker JE, Wilkinson P, *et al.* Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. *Am J Respir Crit Care Med* 2014; 189: 975–982.
32 Mandal P, Chalmers JD, Graham C, *et al.* Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial. *Lancet Respir Med* 2014; 2: 455–463.
33 Muñoz G, De Gracia J, Alvarez A, *et al.* Knowledge and adherence of airway clearance techniques in patients with non-cystic fibrosis bronchiectasis. *Eur Respir J* 2015; 46: Suppl. 59, PA4202.