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A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis

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Abstract

Regular chest physiotherapy is advocated in non-cystic fibrosis bronchiectasis despite little evidence supporting its routine use. This study aimed to establish the efficacy of regular chest physiotherapy in non-cystic fibrosis bronchiectasis compared with no regular chest physiotherapy.

20 patients not practising regular chest physiotherapy were enrolled in a randomised crossover trial of 3 months of twice daily chest physiotherapy using an oscillatory positive expiratory pressure device compared with 3 months of no chest physiotherapy. The primary endpoint was the Leicester Cough Questionnaire (LCQ). Additional outcomes included 24hour sputum volume, $FEV_{1,}$ FVC, midexpiratory flows (FEF_{25-75}), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), exercise capacity, sputum microbiology and St George's Respiratory Questionnaire (SGRQ). The treatment effect was estimated using the differences of the pairs of observations from each patient.

There was a significant improvement in all domains and total LCQ score with regular chest physiotherapy [total score median(IQR)improvement 1.3(-0.17-3.25)units, P=0.002]. 24 hour sputum volume increased significantly with regular chest physiotherapy [2(0-6)mls, P=0.02), as did exercise capacity [40(15-80)metres, P=0.001] and SGRQ total score [7.77(-0.99-14.5)unit improvement, P=0.004). No significant differences were seen in sputum bacteriology, FEV_1, FVC, FEF_{25-75}, MIP or MEP.

Regular chest physiotherapy in non-cystic fibrosis bronchiectasis has small, but significant benefits.

Key words:
Bronchiectasis, Physiotherapy.

Clinical Trial Number:

NCT00816309 (Clinical Trials Database)

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None

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Introduction

In bronchiectasis there is abnormal permanent dilatation of the airways, and the normal mucociliary clearance mechanism is impaired [1, 2]. There are excessive bronchopulmonary secretions and patients have a persistent cough, frequent infective exacerbations and a poor health related quality of life [3, 4].

Chest physiotherapy aims to mobilise secretions and facilitate effective expectoration, providing control of cough and improving airway clearance. It is widely advocated as a mainstay of management for this chronic disease [5]. To date however, there are no randomised controlled trials of chest physiotherapy exclusively in patients with non-cystic fibrosis bronchiectasis [6].

Several different techniques or regimens for airway clearance exist such as postural drainage, autogenic drainage, the active cycle of breathing technique, positive expiratory pressure (PEP), oscillatory PEP devices and high frequency chest wall percussion. Previous small studies in non-cystic fibrosis bronchiectasis have compared various techniques and found no single method to be superior, although patient preference for technique has varied [7, 8].

The aim of this randomised crossover study was to establish the efficacy of routine chest physiotherapy in non-cystic fibrosis bronchiectasis, comparing the effect of twice daily physiotherapy using an oscillatory PEP device with no chest physiotherapy in patients not previously practising regular chest physiotherapy.

Methods

This was a randomised crossover trial of 3 months of twice daily chest physiotherapy followed by a one month washout period compared with 3 months of no chest physiotherapy

in adults with non-cystic fibrosis bronchiectasis not routinely practising chest physiotherapy (October 2007-December 2008, Clinical Trial Registration NCT00816309). Randomisation was determined by computer generation and the study was approved by the Lothian Research Ethics Committee. The primary outcome was patient perceived cough severity measured using the Leicester Cough Questionnaire (LCQ) [9]. Secondary outcomes included 24 hour sputum volume, $FEV_{1,}$ FVC, midexpiratory flows (FEF_{25-75}), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), exercise capacity, sputum microbiology and St George's Respiratory Questionnaire (SGRQ) [10].

Patients

Patients were recruited from the bronchiectasis clinic, Royal Infirmary of Edinburgh, Scotland, UK. Inclusion criteria were: a radiological diagnosis of bronchiectasis using high resolution computed tomography chest scan according to the features described by Naidich et al[11]; chronic sputum expectoration; not carrying out regular chest physiotherapy (for the purposes of this study this was defined as less than two occasions per week); clinically stable disease (defined as no requirement for antibiotics in the 4 weeks preceding study entry). Exclusion criteria were: current smokers; ex-smokers of ≤2years or ex-smokers with a history of ≥10pack years of smoking and emphysema on HRCT; a primary diagnosis of asthma; cystic fibrosis (no CFTR sequence variants present on genotyping); active sarcoidosis or active tuberculosis.

Physiotherapy

Chest physiotherapy was carried out using the oscillatory PEP device "Acapella Choice®" (Smiths Medical ASD, Inc., NH03431, USA). Each patient was trained by the chest physiotherapist (JL Pentland) to complete 3 sets of the following cycle for each treatment session: 10 breaths (each inhaling to three-quarters of the maximum inspiratory capacity then

a 3 second breath hold followed by exhalation to functional residual capacity) and then 2-3 forced expiratory techniques (huffs) or coughs. The frequency/resistance dial (range 1-5) was set at 3 for all participants. This setting was the maximum tolerated by all participants. Patients completed 2 treatment sessions each day (morning and evening, typical duration 20-30 minutes). Compliance and occurrence of any adverse effects (specifically, any haemoptysis or increased use of short acting bronchodilator therapy) were assessed using a diary card which was reviewed monthly during the treatment phase. Technique was reviewed by the chest physiotherapist at monthly intervals during the treatment phase and the devices were retained by the physiotherapist during the non-treatment phase.

Other interventions

Exacerbations requiring antibiotic therapy: An exacerbation was defined as a clinical deterioration with all of the following: increasing cough, increasing sputum volume and worsening sputum purulence [12]. All patients who experienced an exacerbation during the study were reviewed by the study doctor and received fourteen days of antibiotics (prescribed according to sputum bacteriology culture and sensitivities). No additional chest physiotherapy was advised. All were reviewed following completion of antibiotics to ensure recovery.

Routine therapy: any changes made to the patients' usual respiratory medication during the study period were noted.

Endpoints

The study design and assessment timepoints are shown in Figure 1.

Cough Severity and Health Related Quality of Life (HRQL): the LCQ and the SGRQ were completed. Both questionnaires have been validated to reflect impaired HRQL in bronchiectasis [13, 14]. The LCQ is a 19 item self-completed quality of life measure of the impact of cough severity [9]. It has 3 domains: physical (8 items), psychological (7 items)

and social (4 items). The total severity score ranges from 3-21, a lower score indicating a more severe cough. The minimal clinically important difference (MCID) for change is 1.3 units [15]. The SGRQ is a 50 item self-administered health related quality of life questionnaire consisting of 3 components- symptoms (8 items), activity (16 items) and impacts (26 items). The total score ranges from 0-100; a higher score indicates a poorer HRQL. The MCID for the SGRQ is 4 units [14].

Sputum analysis: The total volume of sputum expectorated over a 24hr period was collected in a sterile transparent gradated container. Qualitative and quantitative bacteriology was performed on a separate early morning sample [16].

Pulmonary function tests: FEV_1, FVC, FEF_{25-75}, MIP and MEP [17, 18]. The highest of three technically satisfactory measurements (within 10%) was recorded for each.

Incremental shuttle walk test: an externally paced, 10 metre incremental field walking test [19].

Statistics

Statistical analysis was performed using SPSS for Windows, Version 17 (SPSS inc, Illinois). The primary aim was to detect an improvement in LCQ score. Using the original validation of the LCQ, with 20 patients, a 5% level of significance (2 tailed), a common standard deviation of 0.94 and a power of 80% this would detect a mean difference in LCQ score of 0.63 [9]. Using the validation of the LCQ in non-cystic fibrosis bronchiectasis, with 20 patients, a 5% level of significance (2 tailed), a common standard deviation of 1.1 and a power of 80% this would detect a mean difference in LCQ score of 0.73 [13]. Data was analysed according to the method of Kenward and Jones [20]. The treatment effect was estimated using the differences of the matched pairs of observations from each patient and is presented as median (interquartile range). Treatment differences between regular chest

physiotherapy and no chest physiotherapy were compared using the Wilcoxon test. A 2-tailed P value of <0.05 was considered significant.

Results

Patients

20 outpatients were recruited. Baseline demographics and patient characteristics are detailed in Table 1.

Study Entry- baseline and post-washout

The baseline characteristics for the endpoints at entry to each phase of the study are detailed in Table 2. There was no significant difference in total LCQ score, 24 hour sputum volume, $FEV_{1,}$ FVC, FEF_{25-75}, MIP, MEP, exercise capacity, sputum microbiology and SGRQ score (Table 2) between entry to the first arm of the study (Figure 1, Point 'A') and at the end of the washout period (Figure 1, Point 'C'), prior to entry to the second arm of the study.

Completion and adverse events

All patients completed the study and no adverse effects with the oscillatory PEP device occurred. There were 12 exacerbations affecting 11 patients during the study period (Table 3). No other interventions or changes to patients' care were required throughout the duration of the study.

Treatment differences

There was a significant improvement in all domains of the LCQ and total score see Table 3 and Figure 2.

24 hour sputum volume significantly increased with regular chest physiotherapy compared with no chest physiotherapy (Figure 3). The total SGRQ score improved significantly with regular chest physiotherapy but the only significant improvement seen in the individual domains of the SGRQ score was in the activity domain (Figure 4). Exercise capacity also improved significantly with regular chest physiotherapy (Figure 5) but there were no significant differences seen in sputum bacteriology, FEV_1, FVC, FEF_{25-75}, MIP or MEP, or exacerbation frequency (Table 3).

Discussion

This randomised crossover trial found that twice daily chest physiotherapy in patients with non-cystic fibrosis bronchiectasis not normally practising regular physiotherapy, significantly improves perceived cough severity, increases 24 hour sputum volume, improves exercise capacity and SGRQ score, but has no effect on sputum microbiology, FEV_1, FVC, FEF_{25-75}, MIP, MEP or exacerbation frequency.

Clearance of bronchopulmonary secretions is impaired in patients with bronchiectasis [2]. Mazzaocco et al [21] first explored potential benefits of chest physiotherapy in bronchiectasis patients over 2 decades ago but despite further studies investigating various physiotherapy techniques to aid clearance, there have been no randomised controlled studies exploring the efficacy of regular chest physiotherapy. The primary outcome measured was selected to reflect one of the major goals of management of chronic disease- an improvement in HRQL. Specifically, we wished to assess the impact of the predominant symptom of bronchiectasis- cough severity.

Our study population had clinically significant bronchiectasis. They had an average of 2(1.5-3) exacerbations in the preceding 12 months, over two-thirds were chronically colonised with pathogenic organisms in their sputum and radiologically, 4(3-4.75)lobes were affected with bronchiectasis on CT chest scan and 75% had varicose or cystic dilatation in at least one lobe. Despite this, they did not carry out regular chest physiotherapy prior to the study.

Our study was conducted with twice daily chest physiotherapy over 3 months, as an outpatient. We selected the Acapella Choice® device as the airway clearance technique both for ease of use and based on patient preference from previous studies [8, 22]. Currently, there is no clear evidence for the optimum frequency or duration of airway clearance. However, it is recognised that airway clearance regimens need to be effective without affecting other activities of daily living. We selected a twice daily physiotherapy regimen to account for this

and as previous studies assessing different physiotherapy techniques for non-cystic fibrosis bronchiectasis have achieved compliance with this frequency [8, 23]. Further studies are needed to specifically address the optimal frequency and duration of physiotherapy.

Several adjuncts to physiotherapy currently exist including: bronchodilator therapy which may minimise bronchial hypereactivity and improve airway clearance; inhaled hyperosmolar agents (nebulised hypertonic saline has been shown to yield greater sputum weights and inhaled mannitol which has been shown in small studies to date to aid mucociliary clearance [24, 25]); pulmonary rehabilitation and inspiratory muscle training has previously been shown to improve exercise tolerance [26]. Inhaled mucolytics (recombinant human DNase) on the other hand, although of benefit in cystic fibrosis, is not recommended in non-cystic fibrosis bronchiectasis because it has a significant negative impact on FEV_1 [27]. Our study did not employ any such adjuncts. Further studies are needed to assess efficacy of such techniques in addition to regular chest physiotherapy.

This study did not have a sham arm and instead, we compared twice daily chest physiotherapy using an oscillatory PEP device with no chest physiotherapy. This design was intentional as any type of sham would involve some form of airway clearance. A limitation of this study design, however, is the potential for a placebo effect. The crossover design was used to offer all patients a period of regular chest physiotherapy during the study. There was no carry over effect with the 1 month washout phase.

One of the main goals of long term management of chronic respiratory disease is to improve HRQL and with regular, controlled airway clearance, patient perception of cough severity improved with an increase in score seen in all domains of the LCQ. Since the completion of this study, a 1.3 unit difference in the total LCQ score has been established as a clinically significant change and we observed a median increase of 1.3 units following 3 months of twice daily chest physiotherapy [15]. An open label study by Mutalithas et al found a mean

improvement of 3.1 units in total LCQ score with bronchopulmonary hygiene physical therapy [28]. Importantly, although our study was not powered to detect a change in SGRQ score, we observed that this too improved, with the total score improving beyond its established minimal clinically significant change of 4 units (median improvement of 7.8 units) [14].

A major rationale for chest physiotherapy is to loosen secretions and enhance expectoration. According to previous work by Cecins et al, our study was sufficiently powered to detect a 15% change in 24hour sputum volume and we found that with twice daily chest physiotherapy the mean volume of sputum expectorated over 24 hours increased by 2(0-6)ml [29]. Although the value of 24 hour sputum collections in clinically stable outpatients may be limited by patient compliance and confounded by factors such as swallowed secretions, it is a highly pertinent, non-invasive marker and has been selected as a relevant outcome measure in previous studies assessing other potential long term therapeutic strategies in bronchiectasis including inhaled steroids and long term antibiotics [30-33].

We also observed an increase in the distance achieved during the ISWT following 3 months of twice daily chest physiotherapy. Based on a previous study by Newall et al our patient sample size was powerful enough to detect a significant effect on exercise capacity [26]. This perhaps emphasises the improvement in the activities domain of the SGRQ and that with greater control of cough and clearance of mucus from the airways, exercise capacity also improves.

The benefits observed with regular chest physiotherapy were small however, and we did not find any improvements in the remaining study endpoints. Despite increased sputum expectoration, we observed no change in sputum bacterial load or any improvement in FEV_1, FVC, FEF_{25-75}, MIP, MEP or exacerbation frequency. One previous study of airway clearance techniques in bronchiectasis comparing the Flutter device with the active cycle of breathing

technique found a significant improvement in FEV_1 (0.08L, 95% Confidence Interval 0.01 to 0.15 using the Flutter device), however, this improvement in FEV_1 was not thought to be clinically significant [8]. Our patient cohort had a mean age of 73(72-77)years and with increasing age, there is less airway reversibility, perhaps further limiting the opportunity for any benefit from chest physiotherapy on FEV_1 or FVC. In addition, we found no improvements in the assessment of small airways or inspiratory and expiratory pressures. This may however, be due to the intrinsic variability of such measurements. A previous study by Newall et al in non-cystic fibrosis bronchiectasis patients found MEPs to be impaired but MIPs were within normal range [26]. Our study population was however, older which may explain the difference. Despite the lack of improvements in these measures, exercise capacity significantly increased.

In conclusion, this randomised crossover study found that regular chest physiotherapy in non-cystic fibrosis bronchiectasis has significant benefits compared with no chest physiotherapy. Despite the differences being small, achieving an improvement in functional ability and HRQL is highly relevant to the management of this long-term illness. Larger studies are needed to explore potential benefits on other outcome measures.

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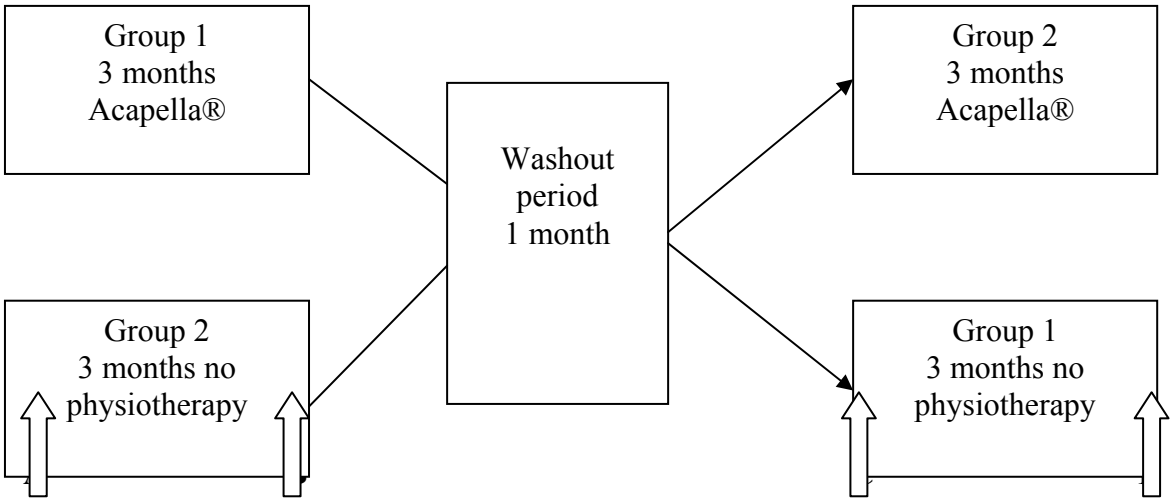


Figure 1. Study protocol. Assessments performed at the start and end of each treatment period. A, B, C and D: assessment time points.

Table 1. Patient Characteristics

Characteristic	n(%) or median(IQR)
Study participants (all outpatients)	20
Male	12(60)
Age (years)	73(72-77)
Ex-smokers	8(40)
Chronic cardiac disease	3(15)
Neurological disease	1(5)
Chronic renal impairment	1(5)
Diabetes Mellitus	0
Inhaled corticosteroid therapy	12(60)
Systemic corticosteroid therapy	0
Long term antibiotic therapy	2(10)
Infective exacerbations requiring antibiotic treatment in preceding 12 months	2(1.5-3)
Lobes affected with bronchiectasis on HRCT	4(3-4.75)
Varicose or cystic dilatation affecting ≥1 lobe	15(75)
Chronically colonised with pathogenic organisms in sputum when stable	14(70)

Pseudomonas aeruginosa	6(42.9)
Haemophilus influenzae	5(35.7)
Staphylococcus aureus	2(14.3)
Moraxella catarrhalis	1(7.1)
Aetiology of bronchiectasis:	
Post-infective	10 (50)
Idiopathic	8 (40)
Inactive allergic bronchopulmonary aspergillosis	1 (5)
Inflammatory Bowel Disease	1(5)

Table 2. Patient characteristics at entry to each phase of study

Characteristic	**Median(IQR) Study Start (Figure 1, Point 'A')**	**Median(IQR) End of Washout Period (Figure 1, Point 'C')**	**P**
Total LCQ Score (units, range 3-21)	16.3(14.1-17.9)	15.9(13.8-19.4)	0.5
24hr sputum volume (ml)	5(1.25-15)	5(1-13.1)	0.3
FEV_1 (L)	1.68(1.25-2.31)	1.72(1.19-2.10)	0.8
(% Predicted)	75.7(48.3-98.1)	68.4(53-107.1)	
FVC (L)	2.64(1.9-3.65)	2.82(1.75-3.5)	0.6
(% Predicted)	79.5(68.2-95.4)	81.6(66.1-95.4)	
FEV_1/FVC	0.63(0.57-0.77)	0.62(0.56-0.82)	0.7
(% Predicted)	87.1(77.6-104.4)	97.0(76.1-120)	
FEF_{25-75} ($L.s^{-1}$)	0.95(0.64-1.54)	1.09(0.54-1.84)	0.96
(% Predicted)	47.5(21.9-64.8)	44.8(24.8-96.4)	
MIP (cmH_2O)	43.5(33.2-72.5)	48(32.5-61.5)	0.2
(% Predicted)	58.5(37.2-77.2)	51.7(31.1-63)	
MEP (cmH_2O)	68.5(58.5-95.2)	67(51-109)	0.3
(% Predicted)	60.9(41.9-83.4)	51.3(38.3-55.7)	

Exercise capacity (m)	220(120-405)	210(137.5-357.5)	1.0
Sputum bacterial load ($cfu.ml^{-1}$)	$3.8x10^6$ ($3.9x10^5$-$3.8x10^7$)	$1.1x10^6$ ($1x10^3$-$1.1x10^8$)	0.6
Total SGRQ Score (units, range 0-100)	41.1(24.6-44.8)	40.4(18.0-52.5)	0.6

Table 3. Treatment differences

Outcome	Twice daily physiotherapy Median(IQR)	No regular physiotherapy Median(IQR)	P
Total LCQ Score Improvement (units)	1.3(-0.17-3.25)	0(-1.5-0.5)	0.002
24hr sputum volume (ml)	2(0-6)	-1(-5-0)	0.02
FEV_1 (L)	-0.01(-0.06-0.08)	-0.01(-0.1-0.11)	0.7
FVC (L)	-0.01(-0.09-0.28)	0.06(-0.08-0.21)	0.9
FEF_{25-75} ($L.s^{-1}$)	-0.02(-0.17-0.16)	0.04(-0.1-0.34)	0.6
MIP (cmH_2O)	-1(-9-7)	5.5(-10-12.5)	0.7
MEP (cmH_2O)	5(-11-25)	8.5(-3.7-19.7)	0.7
Exercise capacity (m)	40(15-80)	0(-10-20)	0.001
Sputum bacterial load ($cfu.ml^{-1}$)	$-1x10^3$ ($-2.78x10^6$-$1.74x10^7$)	$1x10^3$ ($-6.5x10^7$-$6.4x10^6$)	0.72
Total SGRQ Score Improvement (units)	7.8(-0.99-14.5)	-0.7(-2.3-0.05)	0.005
Number of exacerbations	5	7	0.48

Figure 2 Legend.
Change in LCQ individual domain and total scores with physiotherapy and with no physiotherapy. The horizontal lines represent the median and interquartile ranges for each group and the whiskers represent the maximum and minimum. *P=0.002 **P<0.0001 #P=0.02.

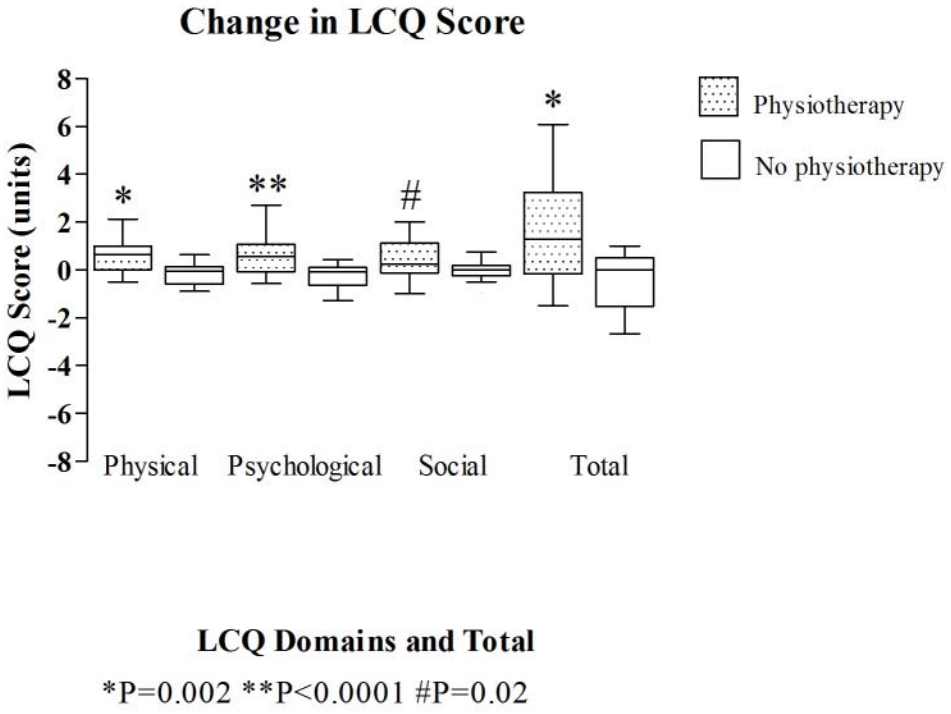


Figure 3 Legend
Change in 24 hour sputum volume with physiotherapy and with no physiotherapy. The horizontal lines represent the median and interquartile ranges and the whiskers represent the maximum and minimum. *P=0.02.

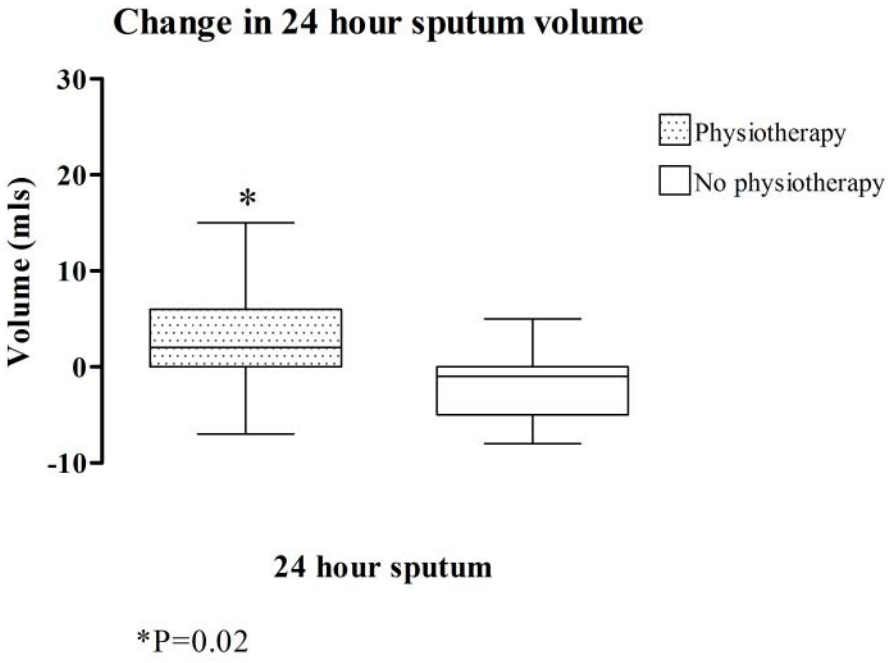


Figure 4 Legend
Change in SGRQ individual domain and total scores with physiotherapy and with no physiotherapy. The horizontal lines represent the median and interquartile ranges for each group and the whiskers represent the maximum and minimum. *P=0.02 **P=0.005.

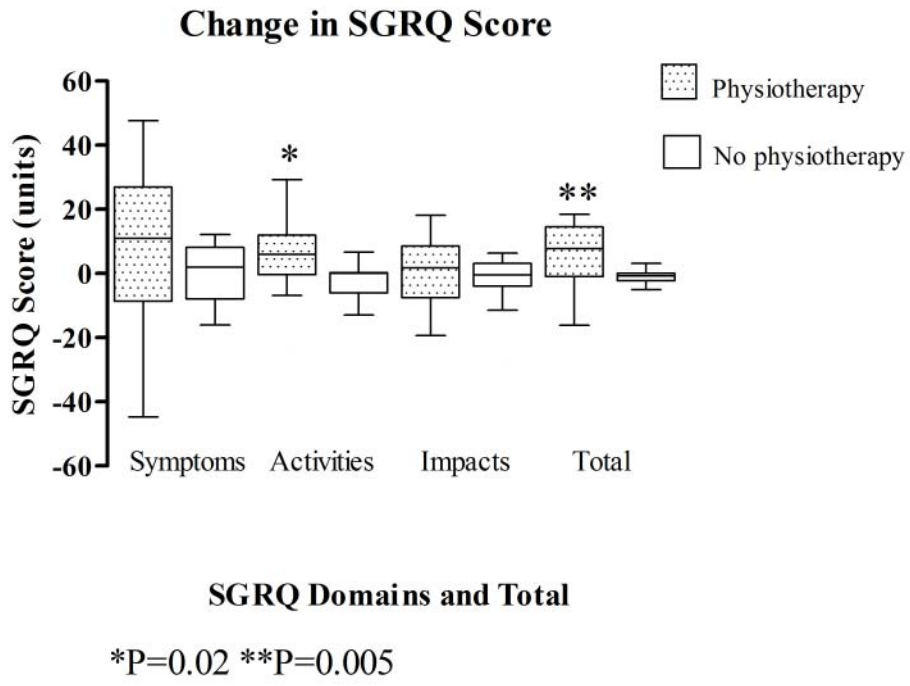
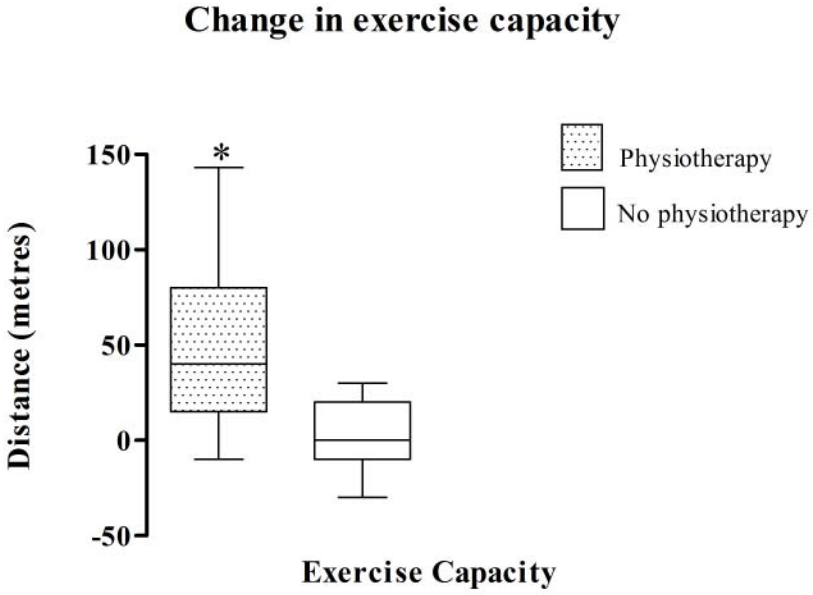


Figure 5 Legend
Change in exercise capacity with physiotherapy and with no physiotherapy. The horizontal lines represent the median and interquartile ranges for each group and the whiskers represent the maximum and minimum. *P=0.001.


Change in exercise capacity
Physiotherapy
No physiotherapy
Distance (metres)
150
100
50
0
-50
*
Exercise Capacity

*P=0.001