BMJ Open

Effects of respiratory physiotherapy in patients with amyotrophic lateral sclerosis: protocol for a systematic review of randomised controlled trials

Karen Pondofe [ID] ,[1] Ana Aline Marcelino,[1] Tatiana Souza Ribeiro,[2] Rodrigo Torres-Castro,[3] Roberto Vera-Uribe,[3] Guilherme AF Fregonezi,[1] Vanessa R Resqueti [ID] [1]

ABSTRACT

Introduction Respiratory muscle weakness and ventilatory failure are common complications in patients with amyotrophic lateral sclerosis (ALS) and may lead to death. Respiratory physiotherapy may improve lung function in this population. This study aims to investigate the effects of respiratory physiotherapy on lung function, cough efficacy and functional status of patients with ALS.

Methods and analysis A protocol was published on the International prospective register of systematic reviews (PROSPERO). The research will cover randomised controlled trials, with no language or publication date restriction, available in the following databases: MEDLINE/PubMed, EMBASE, Cochrane Library, Web of Science and Physiotherapy Evidence Database. The research question will be answered using a search strategy adapted for each database. Searches in databases will be conducted from January 2021 to December 2022. Two authors using the Cochrane risk of bias tool for randomised trials V.2 and Grading of Recommendations, Assessment, Development and Evaluations, respectively, will assess risk of bias and quality of evidence independently. According to the results obtained, data will be reported as a meta-analysis or a narrative report.

Ethics and dissemination No previous ethical approval is required for this publication since data used are already published. Results of this review will be disclosed via peer-reviewed publications and conference presentations.

PROSPERO registration number CRD42021251842.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study presents high-level evidence using randomised controlled trials.
⇒ This protocol allows for peer review and reduces the possibility of bias and duplicates.
⇒ The protocol followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines, and we will use the Grading of Recommendations, Assessment, Development and Evaluations system to analyse the quality of the evidence.
⇒ The limited number of studies available may limit the certainty of the evidence from this systematic review.

worsening prognosis due to accumulation of secretions.[3] Respiratory failure is primarily determined by impaired inspiratory muscle strength associated with loss of motor unit of intercostal and axial muscles.[4]

Forced vital capacity (FVC), maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) are measures of respiratory function easily performed and monitored in the clinical environment. FVC is widely used in patients with ALS and associates with disease progression and survival (FVC of <50% indicates the beginning of respiratory failure). Sniff nasal inspiratory pressure (SNIP) is considered a more accessible alternative than MIP for monitoring respiratory muscle strength.[5] It provides important prognostic information (SNIP of <40 cmH_2O is associated with an average survival of 6 months), and predicts the nocturnal desaturation and respiratory failure in patients with ALS.[6]

Decreased physical function negatively impacts activities of daily living during disease progression. The revised ALS Functional Rating Scale (ALSFRS-R) is strongly related to

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease characterised by loss of cortical, brainstem and spinal motor neurons. The average survival time from symptom onset is 3–5 years; however, survival may be longer in patients with slow disease progression.[1]

Progressive respiratory muscle weakness is one of the main complications affecting patients with ALS.[2] Lung volume reduces over time and leads to ineffective cough and

ALS survival and prognosis is used to assess and monitor the functional status of patients with ALS over time and adds the breathing assessment subcategory.[2 7]

Respiratory system dysfunction ends up being a terminal event for most of these patients,[8] with a reduction in total lung capacity, vital capacity and functional residual capacity.[9] Loss of phrenic nerve function causes diaphragm weakness, which can lead to further complications. Despite the different presentations, most patients have speech impairment and airway clearance due to reduced bulbar muscle coordination.[10]

The combination of inspiratory muscle weakness and reduced chest wall compliance limits the amount of volume needed for an effective cough. Inspiratory capacity represents the volume inspired until the end of the inspiratory phase of cough and is considered the most determining factor for peak cough flow (PCF) (ie, affects length of expiratory muscle and efficiency of subsequent contraction). Also, adequate pressures to develop compressive forces and clear airway secretions are not achieved in the presence of glottic insufficiency.[11–13]

Impaired expiratory muscle contraction also decreases the ability to cough and clear secretions. Physiotherapists should assess and monitor vital capacity, MIP, SNIP or peak expiratory cough flow of patients with ALS at least every 3 months.[14 15] Physiotherapeutic interventions used in individuals with expiratory muscle weakness and secretion retention are lung volume recruitment, and airway clearance techniques with breath stacking, air stacking and manually assisted coughing.[16–19]

In addition, inspiratory muscle training, lung volume recruitment training and mechanical insufflation-exsufflation may also improve survival and should be included in the overall management of ALS.[15 20]

This systematic review will investigate the effects of respiratory physiotherapy on lung function, cough efficacy and functional status of patients with ALS.

REVIEW QUESTION

'What are the effects of respiratory physiotherapy on lung function, cough efficacy and functional status of patients with ALS?'

METHODS AND ANALYSIS

The study will be conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.[21] Searches in databases will be conducted from January 2021 to December 2022.

Eligibility criteria

Randomised controlled trials performed with adult patients, all ages, of both genders and diagnosed with definite, probable, probable laboratory-supported, possible or suspected ALS will be included if full-text or sufficient information about respiratory therapy and results are present. Non-randomised studies found during the
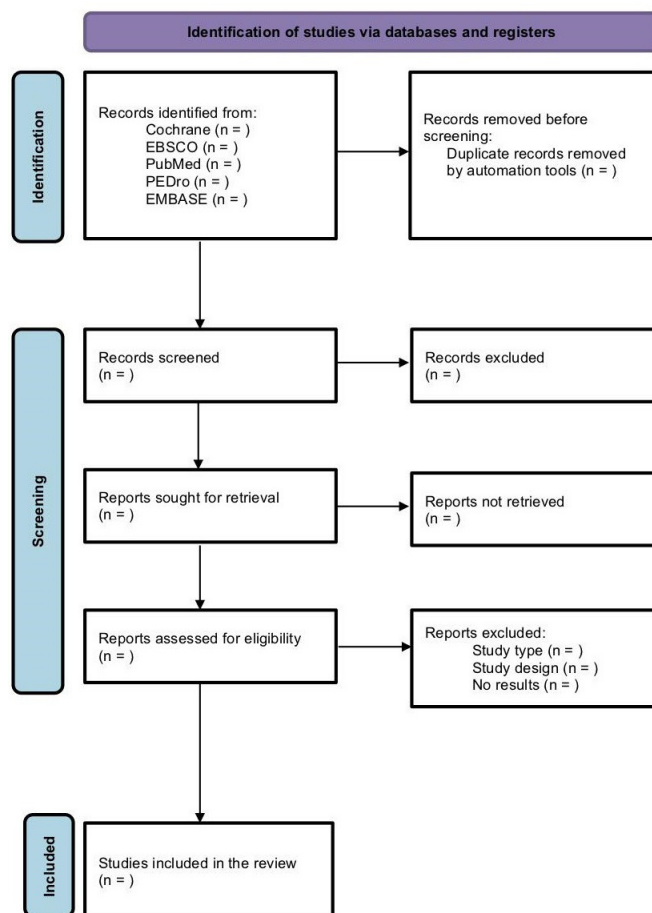
Figure 1 Flow diagram for study selection based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

search will be considered for the 'Discussion' section. Main steps of the search phase will be reported using a PRISMA flow diagram (figure 1). Studies performed with patients with neurodegenerative, cardiac or respiratory diseases associated will be excluded.

Types of interventions
Intervention
Non-invasive respiratory physiotherapy techniques: breathing exercises, respiratory muscle training, air stacking, lung volume recruitment training, non-invasive ventilation, manually assisted cough or mechanical insufflation-exsufflation.

Comparators
Placebo or any combination of other interventions designated as standard treatment or usual conventional care or no intervention will be considered for the control group.

Types of outcome measures
Primary outcomes
► FVC
► Maximal respiratory pressure (MIP and MEP)

Secondary outcomes
► PCF
► SNIP
► Functional status (ALSFRS-R)

Time frame
We will consider assessments performed before and after interventions for a minimum of 3 weeks. We will perform timeline analyses of the evaluated outcomes according to the results found with a maximum of 1 year of follow-up.

Search methods for identification of studies
Electronic searches
The research will cover studies in the following databases with no language or date restriction: MEDLINE/PubMed, EMBASE, Cochrane Library, Web of Science and Physiotherapy Evidence Database (PEDro). The research question will be answered using a designed search strategy following the Cochrane Handbook for Systematic Reviews of Interventions (Lefebvre 2021).

Clinical trials will be searched at the US National Institutes of Health Ongoing Trials Register, WHO International Clinical Trials Registry Platform, European Union Clinical Trials Register and Brazilian Clinical Trials Registry. The initial search strategy will be adapted to each database using Boolean operators, OR and AND.

Non-randomised studies identified from search results will be included in the discussion. A manual search in reference lists of all relevant trials and review articles will be conducted for additional references.

Search strategy
Search strategy will be performed according to the Cochrane Library and adapted for each database (online supplemental file 1).

Data collection and analysis
Selection of studies
Two reviewers (KP and AAM) will independently select studies using eligibility criteria. Studies will be selected by title and abstract and using additional sources. After selection, full texts will be read. Duplicates will be excluded during title and abstract reading or full-text analysis. Decision of reviewers will be blinded, and disagreements will be resolved by discussing with a third reviewer (VRR). Decisions will be recorded and managed using the Rayyan QCRI tool (www.rayyan.ai).

Data extraction and management
The following data will be extracted from selected studies using an extraction form: first author, publication year, study design, sample size, population characteristics, outcome measures, intervention characteristics, statistical results and main conclusions.

Extraction forms for each study will be filled in an excel spreadsheet by the first reviewer (KP) and verified by a second (AAM) reviewer. A third reviewer (VRR) will resolve discrepancies. Missing data will be requested from study authors by email.

Quality assessment of included studies
Risk of bias tool for clinical studies
Risk of bias will be assessed independently by two authors using risk of bias tool V.2. This tool considers random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data (incomplete outcome data), selective description of the outcome (selective reporting) and other possible biases (other bias).

PRISMA-P checklist
The PRISMA-P checklist will be applied to maintain transparency, standardise preparation of this systematic review and accurately summarise information.[21]

Data synthesis and analysis
Selected studies will be analysed and grouped, and results will be arranged in tables. Analyses will be conducted according to the intention-to-treat principle (ie, no missing data). If needed, authors of studies will be contacted to obtain other relevant data. We will base the analyses on available data from all included trials relevant to the comparisons and outcomes of interest. We will include the trials with the most complete data for each outcome. Where data are available from more than one study assessing the same outcome, we will undertake meta-analyses; otherwise, data will be reported in a narrative review. We will use a fixed-effect model to calculate pooled estimates and 95% CIs. If significant heterogeneity exists, we will use a random-effects model. We will use means and SD to calculate the mean difference (MD) and 95% CI for continuous variables. For categorical outcomes, we will relate the numbers reporting an outcome to the numbers at risk in each group to calculate a risk ratio (RR) and 95% CI. If similar outcomes are reported on different scales, we will calculate the standardised mean difference. If data to calculate RRs or MDs are not given, we will use the most detailed numerical data available to calculate the actual numbers or means and SD (eg, test statistics, p values).

Grading the quality of evidence
The quality of evidence for all outcomes will be assessed using the Grading of Recommendations, Assessment, Development and Evaluations[22] Working Group methodology through risk of bias, consistency, objectivity, accuracy and reported bias. The certainty of evidence will be classified as high, moderate, low or very low.

Patient and public involvement
No patient involved.

DISCUSSION
Clinical trials with patients with ALS often present inconsistent results due to the rapid progression of the disease and death. Despite knowledge regarding respiratory physiotherapy techniques for patients with ALS, synthesising and highlighting effective therapies for increasing lung function may help clinical practice; therefore, improving

comfort. This systematic review will strengthen the level of evidence using information from randomised controlled trials and may be used as a guideline for the care of patients with ALS.

Limitations

Possible limitations can be found, such as data heterogeneity, due to differences in intervention protocols and ALS diagnosis subtypes. Impossibility of performing meta-analysis and possible methodological biases since the population studied is highly chronic and susceptible to exacerbations and deaths.

Review status

The study is in the data collection and analysis phase.

Author affiliations

[1]Departamento de fisioterapia, Laboratório de Inovação Tecnológica em Reabilitação e PneumoCardioVascular Lab/HUOL, Hospital Universitário Onofre Lopes, Empresa Brasileira de Serviços Hospitalares (EBSERH), Universidade Federal do Rio Grande do Norte, Natal, Brazil

[2]Departamento de Fisioterapia e Laboratório de Inovação Tecnológica em Saúde (LAIS), Hospital Universitário Onofre Lopes (HUOL), Empresa Brasileira de Serviços Hospitalares (EBSERH), Federal University of Rio Grande do Norte, Natal, Brazil

[3]Department of Physical Therapy, University of Chile, Santiago de Chile, Chile

Twitter Karen Pondofe @karenpondofe and Vanessa R Resqueti @vanessaresqueti

Contributors KP: research concept and study design, literature review, selection of studies, interpretation of data, data collection, writing of the manuscript and reviewing. AAM: selection of studies, data collection, data analysis and interpretation. TR: research concept and study design, and reviewing of the manuscript. RT-C: reviewing the manuscript. RV-U: reviewing the manuscript. GAFF: reviewing the manuscript. VRR: research concept and study design, selection of studies, writing of the manuscript and reviewing.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data sharing not applicable as no datasets generated and/or analysed for this study. Not applicable.

ORCID iDs

Karen Pondofe http://orcid.org/0000-0003-2105-1096

Vanessa R Resqueti http://orcid.org/0000-0003-4817-9364

REFERENCES

1 Rusina R, Ridzoň P, Kulišťák P, *et al*. Relationship between ALS and the degree of cognitive impairment, markers of neurodegeneration and predictors for poor outcome. A prospective study. *Eur J Neurol* 2010;17:23–30.

2 Cedarbaum JM, Stambler N, Malta E, *et al*. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. *J Neurol Sci* 1999;169:13–21.

3 Rokadia HK, Adams JR, McCarthy K, *et al*. Cough augmentation in a patient with neuromuscular disease. *Ann Am Thorac Soc* 2015;12:1888–91.

4 Sarmento A, Resqueti V, Dourado-Júnior M, *et al*. Effects of air stacking maneuver on cough peak flow and chest wall compartmental volumes of subjects with amyotrophic lateral sclerosis. *Arch Phys Med Rehabil* 2017;98:2237–46.

5 Niedermeyer S, Murn M, Choi PJ. Respiratory Failure in Amyotrophic Lateral Sclerosis. *Chest* 2019;155:401–8.

6 Morgan RK, McNally S, Alexander M, *et al*. Use of Sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. *Am J Respir Crit Care Med* 2005;171:269–74.

7 Chiò A, Calvo A, Ilardi A, *et al*. Lower serum lipid levels are related to respiratory impairment in patients with ALS. *Neurology* 2009;73:1681–5.

8 Pinto S, Swash M, de Carvalho M. Respiratory exercise in amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis* 2012;13:33–43.

9 Benditt JO. Respiratory care of patients with neuromuscular disease. *Respir Care* 2019;64:679–88.

10 Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003;168:10–48.

11 Kravitz RM. Airway clearance in Duchenne muscular dystrophy. *Pediatrics* 2009;123:S231–5.

12 Smith JA, Aliverti A, Quaranta M, *et al*. Chest wall dynamics during voluntary and induced cough in healthy volunteers. *J Physiol* 2012;590:563–74.

13 Lo Mauro A, Aliverti A. Physiology of respiratory disturbances in muscular dystrophies. *Breathe* 2016;12:318–27.

14 Miller RG, Brooks BR, Swain-Eng RJ, *et al*. Quality improvement in neurology: amyotrophic lateral sclerosis quality measures: report of the quality measurement and reporting Subcommittee of the American Academy of Neurology. *Neurology* 2013;81:2136–40.

15 National Institute for Health and Care Excellence. *Motor neurone disease: assessment and management*. London, UK: Clinical Guideline NG42, NICE, 2016.

16 Dal Bello-Haas V. Physical therapy for individuals with amyotrophic lateral sclerosis: current insights. *Degener Neurol Neuromuscul Dis*;8:45–54.

17 Cleary S, Misiaszek JE, Kalra S, *et al*. The effects of lung volume recruitment on coughing and pulmonary function in patients with ALS. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2013;14:111–5.

18 Sancho J, Servera E, Bañuls P, *et al*. Effectiveness of assisted and unassisted cough capacity in amyotrophic lateral sclerosis patients. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2017;18:498–504.

19 Kaminska M, Browman F, Trojan DA, *et al*. Feasibility of lung volume recruitment in early neuromuscular weakness: a comparison between amyotrophic lateral sclerosis, myotonic dystrophy, and postpolio syndrome. *PM&R* 2015;7:677–84.

20 Macpherson CE, Bassile CC. Pulmonary physical therapy techniques to enhance survival in amyotrophic lateral sclerosis: a systematic review. *J Neurol Phys Ther* 2016;40:165–75.

21 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4.

22 Guyatt G, Oxman AD, Akl EA, *et al*. Grade guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.