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https://doi.org/10.1002/14651858.CD012482

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Mechanical cough augmentation techniques in amyotrophic lateral sclerosis/motor neuron disease (Protocol)

Rafiq MK, Bradburn M, Mustfa N, McDermott CJ, Annane D.


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Mechanical cough augmentation techniques in amyotrophic lateral sclerosis/motor neuron disease

Muhammad K Rafiq1, Michael Bradburn2, Naveed Mustfa3, Christopher J McDermott4, Djillali Annane5

1Academic Neurology Unit, University of Sheffield, Sheffield, UK. 2Clinical Trials Research Unit, University of Sheffield, Sheffield, UK. 3Department of Respiratory Medicine, Royal Stoke University Hospital, University Hospital of North Midlands, Stoke-on-Trent, UK. 4Sheffield Institute for Translational Neuroscience (SITraN), University of Sheffield, Sheffield, UK. 5Critical Care Department, Hôpital Raymond Poincaré, Assistance Publique - Hôpitaux de Paris, Garches, France

Contact address: Muhammad K Rafiq, Academic Neurology Unit, University of Sheffield, Sheffield, UK. m.k.rafiq@sheffield.ac.uk

Editorial group: Cochrane Neuromuscular Group.


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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of mechanical insufflator/exsufflator (MI-E) and the breath-stacking technique for reducing morbidity and mortality and enhancing quality of life in people with amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND).

BACKGROUND

Description of the condition

Amyotrophic lateral sclerosis (ALS), which is also known as motor neuron disease (MND), is a progressive, neurodegenerative condition that causes significant disability and shortens life expectancy. Two to three new cases per 100,000 people occur each year, with a prevalence of five to seven affected individuals per 100,000 population (del Aguila 2003; Kiernan 2011). There is no cure and average life expectancy is two to three years from symptom onset (Alonso 2009). The only available disease-modifying therapy, riluzole, has a modest effect on the disease course (Paillisse 2005); however, supportive measures delivered via a multidisciplinary team approach have been demonstrated to improve outcomes (Aridegbe 2013). In this regard, management of respiratory symptoms is an important facet of care for people with ALS. Non-invasive ventilation (NIV) has the largest impact on survival and quality of life of any therapeutic intervention for ALS reported to date (Bourke 2006). A common and distressing symptom faced by people with ALS with respiratory muscle weakness and bulbar (laryngeal) dysfunction is the inability to cough well enough to mobilise and expel secretions from the airway (Lahrmann 2003; Servera 2003). Inspiratory muscle weakness limits the depth of the pre-cough inspiration, bulbar weakness impairs glottic closure, and expiratory muscle weakness reduces intrathoracic expiratory pressure, all or any of which are associated with ALS and reduce cough flow and efficacy (Hadjikoutis 1999). In addition, neuromuscular bulbar dysfunction impairs swallowing and increases the risk of aspiration of food or liquid. Peripheral atelectasis secondary to respiratory muscle weakness creates a susceptibility to...
increased airway and lung secretions. These factors combined may increase the requirement to cough. Cough effectiveness is suboptimal when peak cough flow (PCF) is less than 270 L/min (Toussaint 2009). An effective cough protects against respiratory tract infections, which are the most common cause of hospital admission in people with respiratory muscle weakness (Bach 1997; Lechtzin 2001; Servera 2003). During chest infections, already impaired pulmonary function is further compromised by airway mucus accumulation, fatigue and worsening dysfunction of weak respiratory muscles. Secretions that plug the airway can result in partial or complete collapse of the lung contributing to acute or acute-on-chronic respiratory failure, which remains the most common cause of death in ALS (Corcia 2008; Kiernan 2011).

Traditionally, manual chest physiotherapy (MCP) has been used to assist recovery during chest infections. MCP requires considerable time and effort by the person with ALS and a trained therapist. Furthermore, MCP alone is unlikely to be sufficient to clear airway secretions when the person has advanced respiratory muscle weakness. Hence mechanical aids may be required to enhance cough.

**Description of the intervention**

Manual insufflator devices (used for the breath-stacking technique) and mechanical insufflator/exsufflator (MI-E, coughAssist) devices, have been used as non-invasive aids to assist cough in neuromuscular disorders (Mustfa 2003; Tzeng 2000). MI-E was introduced during the polio epidemic to help people supported by 'iron lung' ventilators (Bach 1992; Bach 1993a; Barach 1993; Barach 1954). Tzeng and Bach developed and followed up use of a home protocol combining NIV with cough assist techniques in people with ALS. They concluded that people using the protocol had significantly fewer hospitalisations per year; days hospitalised reduced from a mean (standard deviation (SD)) of 20.14 ± 41.15 days per year to 1.43 ± 3.71 days per year per person upon the introduction of MI-E (Tzeng 2000). Further physiological studies demonstrated that MI-E achieved higher PCF rates than other methods of cough augmentation (Anderson 2005; Chatwin 2003; Mustfa 2003; Winck 2004; ). The American Academy of Neurology Practice Parameters recommended the use of MI-Es for people with neuromuscular respiratory weakness, particularly during an acute chest infection (Miller 2009). In the absence of a randomised controlled trial (RCT), however, evidence to support the use of MI-E was considered weak (level 3). Evidence in favour of the breath-stacking technique is even weaker. Significantly increased PCFs have been demonstrated in people with neuromuscular disease, who were able to breath-stack successfully (Armstrong 2009; Cleary 2013; Kang 2000).

MI-E is an electronic machine which simulates cough by delivering alternate cycles of positive and negative pressure to the airways through a face mask. It can also be used with a mouthpiece or tracheostomy. The positive pressure increases inspiratory pressure, and the negative pressure increases expiratory pressure (Morrow 2013). The machine can generate a pressure of up to +60/-60 cmH2O. The volume of air and PCF exsufflated using MI-E are comparable to those expelled during normal adult coughing (Bach 1993b).

The breath-stacking technique uses a bag valve mask (BVM, or self-inflating resuscitator) to deliver large breath volumes to the person with ALS via a suitable interface. The device has a one-way valve, allowing air flow into the airway to enhance inspiratory effort. The lungs are inflated as fully as possible by stacking successive breaths without expiration i.e. holding the successively inspired air volume against a closed glottis. Once the lungs are maximally inflated, the person releases the compressed air volume under expiratory muscle force, thus generating a cough with lung and chest wall recoil. Lechtzin 2006 demonstrated in a prospective study that supra-maximal lung inflation improves lung compliance, possibly by correcting atelectasis (partially collapsed lung tissue due to reduced air flow). Another study showed that PCF improved by 50 L/min after treatment with breath-stacking, and this improvement was sustained for about 30 minutes (Armstrong 2009). Breath-stacking has been shown to improve inspiratory volume, correct atelectasis, enhance rib cage movement and improve voice volume (Cleary 2009). However, this is a difficult technique requiring reasonable respiratory muscle strength and co-ordination. Furthermore, people with bulbar muscle weakness may find it impossible to retain the volumes of air acquired by stacking, due to inability to close the glottis. Breath-stacking can be combined with a chest compression, abdominal thrust, or both, synchronised with the person’s coughing following maximal insufflation (Bach 2004).

**Why it is important to do this review**

Although the above-mentioned observational studies have confirmed the safety and efficacy of cough augmentation techniques and there is clinical experience of several decades, the use of these techniques has not been systematically incorporated into the care of people with ALS. A systematic review of evidence demonstrating efficacy and benefit of cough augmentation techniques would strengthen the case for funding of these interventions for people with ALS. This review will examine current evidence on the effects of MI-E and the breath-stacking technique on pulmonary morbidity, quality of life and survival in people with ALS-related respiratory failure.

**How the intervention might work**

**OBJECTIVES**

Mechanical cough augmentation techniques in amyotrophic lateral sclerosis/motor neuron disease (Protocol)

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To assess the effects of mechanical insufflator/exsufflator (MI-E) and the breath-stacking technique for reducing morbidity and mortality and enhancing quality of life in people with amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND).

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include randomised controlled trials (RCTs) and quasi-RCTs. Quasi-randomised trials are studies that allocate participants to groups using methods that are partly systematic, for example by alternation, use of a case record number, or date of attendance. We will include studies reported as full text, those published as abstract only, and unpublished data. There will be no restrictions as to language.

**Types of participants**

We will include adults of all age groups with a diagnosis of ALS and neuromuscular respiratory failure. The participants must fulfill the El Escorial criteria for definite ALS, clinically probable ALS, or clinically probable laboratory-supported ALS.

**Types of interventions**

We will include trials comparing:

1. MI-E with other cough augmentation techniques, standard care or no intervention; and
2. breath-stacking with other cough augmentation techniques, standard care or no intervention.

We will include trials that incorporate co-interventions (for example, non-invasive ventilation (NIV)) provided that the co-interventions are offered to each group equally.

**Types of outcome measures**

**Primary outcomes**

1. Number of chest infections requiring antibiotic treatment during the follow-up period.
2. Number of hospital admissions for chest infections during the follow-up period.

**Secondary outcomes**

1. Change in quality of life (assessed by a validated measure such as SF36 or sleep apnoea quality of life index) from baseline to 12 months.
2. Survival at 12 months.
3. Change in impact on the primary carer (assessed by a validated measure such as the Carer Strain Index) from baseline to 12 months.
4. Change in peak cough flow (assessed by peak flow meter) and forced vital capacity (FVC) expressed as percentage predicted from baseline to 12 months.
5. Adverse events, reported as any adverse events, adverse events which lead to discontinuation of treatment and serious adverse events, that is, those which are fatal, life-threatening, or require prolonged hospitalisation.

**Search methods for identification of studies**

**Electronic searches**

We will identify trials from the Cochrane Neuromuscular Disease Group Specialised Register, which is maintained by the Information Specialist for the Group; the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; and EMBASE. The draft MEDLINE strategy is in Appendix 1.

We will also conduct a search of the US National Institutes of Health Clinical Trials Registry, ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

**Searching other resources**

We will search reference lists of all relevant primary studies and review articles for additional references. We will search relevant manufacturers’ websites for trial information.

**Data collection and analysis**

**Selection of studies**

Two review authors (MKR and NM) will independently screen titles and abstracts of all the studies we identify from the search for inclusion, and code them as ‘retrieve’ (eligible or potentially eligible/unclear) or ‘do not retrieve’. We will obtain the full-text study reports/publications and two review authors (MKR and NM) will
Data extraction and management

For study characteristics and outcome data we will use a data extraction form that has been piloted on at least one study in the review. One review author (MKR and NM) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline characteristics, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported. We will collect data on attrition, loss to follow-up and the extent of missing data from each study.
5. Funding for trial, and notable conflicts of interest of trial authors.

Two review authors (MKR and NM) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third person (CJM). One review author (MKR) will transfer data into Review Manager (RevMan 2014). Extraction and input of all outcome data will be verified by the statistician (MB). A second review author (CJM) will spot-check study characteristics for accuracy against the trial report. When reports require translation, the translator will extract data directly using a data extraction form, or authors will extract data from the translation provided. Where possible a review author will check numerical data in the translation against the study report.

Assessment of risk of bias in included studies

Two review authors (MKR and NM) will independently assess risk of bias for each study, with disagreements resolved by discussion or by involving another author (CJM). The criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) are as follows.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low or unclear risk, and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. Given the nature of these interventions we envisage blinding of study participants (item 3) to be unattainable. We will summarise the 'Risk of bias' judgements across different studies for each of the outcomes. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a triallist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as risk ratios (RRs), survival outcomes as hazard ratios (HRs) and continuous data as mean difference, or standardised mean difference for results across studies with outcomes that are conceptually the same but measured in different ways. We will enter data presented as a scale with a consistent direction of effect.

We will undertake meta-analyses only where this is meaningful; that is, if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. Where multiple trial treatment arms are reported in a single trial, we will include only the eligible arms. If two comparisons (e.g. treatment A versus placebo and treatment B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

For cross-over trials, we will include data from the whole follow-up period. For studies with more than one intervention group, we will include each group separately in the meta-analysis.
Dealing with missing data
We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (for example when a study is available as an abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity
We will use the $I^2$ statistic to measure heterogeneity among the trials in each analysis. If we identify substantial unexplained heterogeneity we will report it and explore possible causes by prespecified subgroup analysis. We will use the rough guide to interpretation that is outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*:
- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity; and
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases
We will assess the potential for bias using the 'Risk of bias' tool (as noted previously). We will produce a funnel plot to investigate possible small study biases, bearing in mind its limitations if (as expected) few trials are identified.

Data synthesis
We will be mindful of the fact that ALS is a heterogeneous condition; there are at least three sub-types and each sub-type has a difference prognosis. As stated above, we will ensure that the participants fulfill the El Escorial criteria for definite ALS, clinically probable ALS, or clinically probable laboratory-supported ALS. If included trials are sufficiently similar and combining their data makes sense clinically, we will pool results in a meta-analysis using both fixed-effect and random-effects models, and assess their consistency. Where data cannot be pooled, the results will be described in a narrative form. Given the likely small number of trials, we will describe inconsistencies qualitatively but if data allow will apply meta-regression methodologies. If the review includes more than one comparison, which cannot be included in the same analysis, we will report the results for each comparison separately.

'Summary of findings' table
We will create a 'Summary of findings' table using the following outcomes (see *Types of outcome measures*).

1. Pulmonary morbidity (number of chest infections treated in hospital and in the community).
2. Change in quality of life.
4. Change in impact on the primary carer.
5. Change in peak cough flow and FVC.
6. Adverse events.

Two review authors will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to independently assess the quality of a body of evidence (studies that contribute data for the prespecified outcomes). They will resolve disagreements by discussion, involving other review authors if necessary. The review authors will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEproGDT software (GRADEproGDT 2015). We will justify all decisions to down- or up-grade the quality of studies using footnotes and we will make comments to aid readers’ understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity
We plan to carry out the following subgroup analysis (depending on the availability of sufficient reported data).
1. Normal to mildly impaired bulbar function and moderate to severely impaired bulbar function.

We will use the following outcomes in subgroup analyses.
1. Average number of chest infections requiring antibiotic therapy per year.
2. Survival.

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis
We plan to carry out the following sensitivity analyses.
1. Repeat the analysis excluding unpublished studies (if there are any).
2. Repeat the analysis excluding studies at high risk of bias (for example, quasi-randomised studies, at high risk of selection bias).
3. If there is one or more very large studies, repeat the analysis excluding them to look at how much they dominate the results.

Reaching conclusions
We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline the remaining uncertainties in the area.
ACKNOWLEDGEMENTS

We thank Ruth Brassington, Managing Editor, Cochrane Neuromuscular Disease Group.

This project was supported by the National Institute for Health Research (NIHR) via Cochrane Infrastructure funding to the Cochrane Neuromuscular Disease Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS) or the Department of Health. The Cochrane Neuromuscular Disease Group is also supported by the MRC Centre for Neuromuscular Disease.

REFERENCES

Additional references

Alonso 2009

Anderson 2005

Aridegbe 2013

Armstrong 2009

Bach 1992

Bach 1993a

Bach 1993b

Bach 1997

Bach 2004

Barach 1953

Barach 1954

Bourke 2006

Chatwin 2003

Cleary 2009
Cleary 2013

Corcia 2008

Lahrmann 2003

Lechtzin 2001

Lechtzin 2006

Miller 2009

Morrow 2013

Mustfa 2003

Paillisse 2005

RevMan 2014 [Computer program]

Servera 2003

Toussaint 2009

Tzeng 2000

Winck 2004

* Indicates the major publication for the study
APPENDICES

Appendix 1. MEDLINE (OvidSP) search strategy

DRAFT STRATEGY
Database: Ovid MEDLINE(R) <1946 to November Week 1 2014>
Search Strategy:
--------------------------------------------------------------------------------
1 randomized controlled trial.pt. (399610)
2 controlled clinical trial.pt. (90639)
3 randomized.ab. (294664)
4 placebo.ab. (154739)
5 drug therapy.fs. (1783968)
6 randomly.ab. (206726)
7 trial.ab. (306795)
8 groups.ab. (1313596)
9 or/1-8 (3363515)
10 exp animals/ not humans.sh. (4092437)
11 9 not 10 (2865537)
12 exp Motor Neuron Disease/ (20976)
13 (moto$1 neuron$1 disease$1 or moto neuron$1 disease$1).mp. (6513)
14 amyotrophic lateral sclerosis.mp. (17523)
15 ((Lou Gehrig$1 adj5 syndrome$1) or (Lou Gehrig$1 adj5 disease$1)).mp. (112)
16 charcot disease.tw . (18)
17 or/12-16 (25416)
18 insufflation/ (1607)
19 (insufflation or exsufflation).mp. (5268)
20 (cough adj1 assist$).tw . (85)
21 (cough adj2 augment$).tw . (37)
22 MI-E.mp. (30)
23 lung volume recruitment.mp. (47)
24 breath stacking.mp. (14)
25 or/18-24 (5407)
26 11 and 17 and 25 (15)
27 remove duplicates from 26 (13)

CONTRIBUTIONS OF AUTHORS

MKR wrote the protocol. NM and CJM critically reviewed the protocol. MB made a substantial contribution as a statistician.

DECLARATIONS OF INTEREST

MR: none known
MB: none known
NM: none known

CJM is the Chief Investigator on an NIHR Health Technology Assessment (HTA) and Motor Neurone Disease Association (MND)-funded study investigating the role of diaphragmatic pacing in ALS. This study has also received support from Synapse Biomedical in the form of pacing devices provided at no cost and technical support relating to device implantation and malfunction. CJM is a co-investigator on an MND-funded trial of cough assist devices in MND.
SOURCES OF SUPPORT

Internal sources

• School of Health and Related Research, UK.

External sources

• Motor Neurone Disease Association, UK.
• Wellcome Trust, UK.
• National Institute for Health Research, UK.