INPLASY PROTOCOL

To cite: Gutiérrez-Arias et al. Effectiveness of neuromuscular electrostimulation in adults with chronic obstructive pulmonary disease on mechanical ventilation. Protocol of a systematic review and meta-analysis. Inplasy protocol 202140091. doi: 10.37766/inplasy2021.4.0091

Received: 17 April 2021

Published: 18 April 2021

Corresponding author:
Ruvistay Gutiérrez-Arias

ruvistay.gutierrez@gmail.com

Author Affiliation:
Unidad de Paciente Crítico, Instituto Nacional del Tórax & Escuela de Kinesiología, Universidad Andrés Bello.

Support: **None.**

Review Stage at time of this submission: **Preliminary searches.**

Conflicts of interest:
None declared.

Effectiveness of neuromuscular electrostimulation in adults with chronic obstructive pulmonary disease on mechanical ventilation. Protocol of a systematic review and meta-analysis

Gutiérrez-Arias, R[1]; Jalil, Y[2]; Fuentes-Aspe, R[3]; Serón, P[4].

Review question / Objective: **Is the application of surface electrical stimulation an effective intervention, in terms of functional independence, muscle strength, duration of mechanical ventilation and other secondary outcomes, in adults with chronic obstructive pulmonary disease requiring mechanical ventilation support?**
Condition being studied: **People with COPD are characterized by airflow limitation, which is usually associated with significant limb muscle dysfunction. Both conditions can cause varying degrees of dyspnea and fatigue, symptoms that can negatively impact health-related quality of life. When people with COPD present some level of exacerbation of their disease (AECOPD), they may require hospitalization and even ventilatory support such as non-invasive mechanical ventilation (NIV), a key intervention in the management of these patients, which can turn into invasive (IMV) in more severe cases. Considering the previous condition of people with COPD and the complications of critical illness associated to ventilatory support, these patients have an unfavorable functional prognosis.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 April 2021 and was last updated on 18 April 2021 (registration number INPLASY202140091).

INTRODUCTION

Review question / Objective: **Is the application of surface electrical stimulation an effective intervention, in terms of functional independence, muscle strength, duration of mechanical ventilation and other secondary outcomes, in adults with**

chronic obstructive pulmonary disease requiring mechanical ventilation support?

Rationale: Advances in medical care have prolonged the survival of critically ill patients, which is associated with increased time to resolution of critical illness leading to increased neuromuscular and respiratory complications. Among neuromuscular complications, ICU-acquired weakness is one of the most common, which may occur in up to 100% of critically ill persons. This impairment is directly associated with prolonged mechanical ventilation, which may lead to mechanical ventilation-induced lung injury, mechanical ventilation-associated pneumonia and diaphragmatic muscle injury, adverse effects that may result in long hospital stay associated to poor functional state, impaired health-related quality of life and the consequent increased health costs even after discharge. All these complications could be exacerbated in people with chronic obstructive pulmonary disease (COPD), as they are subjects with relevant baseline respiratory and muscular impairment, which could lead to worse outcomes. One of the strategies that has been proposed to limit muscle deterioration in mechanically ventilated subjects is neuromuscular electrical stimulation (NMES), which can be applied in awake subjects with the possibility of cooperating as well as in sedated subjects. While this strategy has shown promising results in the general population with critical illness undergoing mechanical ventilation, outcomes in people with COPD reported in primary studies are discrepant and inconclusive, so it is necessary to summarize the findings of these primary studies in order to determine the effectiveness of NMES in COPD adults undergoing either invasive or non-invasive ventilatory support.

Condition being studied: People with COPD are characterized by airflow limitation, which is usually associated with significant limb muscle dysfunction. Both conditions can cause varying degrees of dyspnea and fatigue, symptoms that can negatively impact health-related quality of life. When people with COPD present some level of exacerbation of their disease (AECOPD), they may require hospitalization and even ventilatory support such as non-invasive mechanical ventilation (NIV), a key intervention in the management of these patients, which can turn into invasive (IMV) in more severe cases. Considering the previous condition of people with COPD and the complications of critical illness associated to ventilatory support, these patients have an unfavorable functional prognosis.

METHODS

Search strategy: The controlled (e.g. Mesh and EMTREE) and natural language will be adjusted according to the database and platform used. The following is the search strategy to be used in MEDLINE through the Pubmed platform: ((((((("Pulmonary Disease, Chronic Obstructive"[Mesh]) OR ("Bronchitis, Chronic"[Mesh])) OR ("Pulmonary Emphysema"[Mesh])) OR ("Lung Diseases, Obstructive"[Mesh])) OR ((obstruct*) AND (((((((pulmon*) OR (lung*)) OR (lung*)) OR (airway*)) OR (airflow*)) OR (bronch*)) OR (respirat*)))) OR (((((COPD) OR (AECOPD)) OR (COAD)) OR (COBD)) OR (AECB))) AND ((((((("Respiration, Artificial"[Mesh]) OR ("Positive-Pressure Respiration"[Mesh])) OR ("Noninvasive Ventilation"[Mesh])) OR ("Ventilators, Mechanical"[Mesh])) OR ("Intubation, Intratracheal"[Mesh])) OR (((((artificial) OR (mechanical)) OR ("non-invasive")) OR (noninvasive)) AND ((ventilat*) OR (respirat*)))) AND ((((((("Electric Stimulation Therapy"[Mesh]) OR ("Transcutaneous Electric Nerve Stimulation"[Mesh])) OR ("Electric Stimulation"[Mesh])) OR (((neuromuscular) OR (functional)) AND (electric*))) OR ((((electrotherap*) OR (electromyostimulation)) OR (electrostimulation)) OR ((electric*) AND (stimulation)))) OR (((NMES) OR (FES)) OR (TENS))).

Participant or population: We will include primary studies that consider adult subjects (18 years or older) with COPD, and who because of an exacerbation of their

disease underwent ventilatory support such as NIV or IMV.

Intervention: Primary studies that consider electrical stimulation as an intervention, i.e. NMES, functional electrical stimulation (FES), transcutaneous electrical nerve stimulation (TENS) or other, shall be included. This intervention will be understood as the application of a train of electrical pulses to a motor nerve via surface electrodes, causing contraction of the associated muscle, regardless of the frequency, pulse width, intensity, time of application and muscle to be stimulated (upper limbs, lower limbs, and thoracic or abdominal muscles).

Comparator: Primary studies that subjected the control group to usual care or sham NMES/FES/TENS will be included. In case of other interventions applied to both the intervention and control groups, such as early mobilization, they must be delivered in a similar way to both groups for the study to be eligible.

Study designs to be included: The primary studies to be included should be controlled clinical trials, either randomized controlled trials (RCTs) or non-RCTs. The publication status of studies will not limit their inclusion in our review.

Eligibility criteria: The primary studies to be included must comply with the characteristics explained in the section "Participant or population", "Intervention", "Comparator" and "Study design to be included". In addition, studies must report on at least one of the primary or secondary outcomes listed below (see section "Primary outcomes" and "Additional outcomes").

Information sources: The databases to be consulted will be MEDLINE, Embase, the Cochrane Central Register of Clinical Trials (CENTRAL) and CINAHL. In addition, we will search clinical trial protocol registers (https://www.who.int/clinical-trials-registry-platform and https://clinicaltrials.gov/), grey literature (http://www.opengrey.eu/search/), and handsearch the reference list of similar systematic reviews and primary studies included in our review.

Main outcome(s): We will consider three primary outcomes: 1) Functional independence: assessed by generic or specific validated instruments, such as the Functional Status Score for the Intensive Care Unit (FSS-ICU); 2) Muscle strength: assessed by a manual test, e.g. the Medical Research Council muscle strength assessment, or by a specific assessment, e.g. assessment of grip strength through dynamometry; 3) Duration of mechanical ventilation (MV): reported as the number of days between the start of ventilatory support (NIV or IMV) and weaning consolidation.

Additional outcome(s): Additionally we will consider the following secondary outcomes: 1) Duration of weaning of MV: reported as the number of days between the start of the weaning process and its consolidation; 2) Intensive Care Unit (ICU) length of stay: reported as the number of days between admission and discharge from the ICU; 3) Length of hospital stay: reported as the number of days between the start of ventilatory support and hospital discharge; 4) Dyspnea: measured by any specific or generic validated scale, e.g. Medical Research Council dyspnea scale or Borg scale; 5) Leg fatigue: measured by any specific or generic validated scale, e.g. visual analogue scale (VAS). 6) Functional exercise capacity at discharge: measured by any field test, e.g. distance walked in the 6-Minute Walk Test (6MWT); 7) Maximal exercise capacity at discharge: measured by any laboratory test where the maximum or peak oxygen consumption (VO2max or VO2peak) is estimated, e.g. cardiopulmonary exercise test on a cycloergometer; 8) Quality of life: measured by any specific or validated generic questionnaire, e.g. St. George's Respiratory Questionnaire (SGRQ); 9) Physical activity at discharge: measured through generic or specific validated questionnaires, e.g. International Physical Activity Questionnaire (IPAQ), or some other standardized test such as the step count;

10) Adverse effects: measured through the incidence of any adverse effects directly related to the application of the intervention, such as allergy in the area of application of electrostimulation, pain, or other more serious effects such as arrhythmias.

Data management: Two reviewers will read the titles and abstracts of studies identified through our search strategy to determine whether they meet our eligibility criteria and rate them as "included", "excluded" or "maybe". Studies categorized as "included" or "maybe" will be reviewed in full text to ultimately determine whether they are included in our review. For this stage of our study we will use the Rayyan® application. The extraction of information from the studies will be done by two reviewers using a standardized form. Basic information such as population, intervention and comparator characteristics, as well as details of study design and outcome data will be extracted. In the event that more than one publication exists for a study, these will be grouped together, and the most complete version will be selected for final analysis and extraction of outcome data. Both the study selection and data extraction stages will be conducted independently and blinded. Disagreements will be resolved by consensus or, ultimately, by the decision of a third reviewer.

Quality assessment / Risk of bias analysis: The risk-of-bias assessment of the estimation of outcomes reported by the included studies will be performed using the Cochrane risk-of-bias tool 2 (RoB 2). For each reported outcome, this tool considers the (1) bias arising from randomization process, (2) bias due to deviations from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result. According to this tool, studies will be categorized as “low risk”, “some concerns” or “high risk” of bias. In addition, the overall certainty of the evidence will be assessed using the GRADE approach, which considers the risk of bias, inconsistency of results, indirect evidence, imprecision and reporting bias. Two independent and blinded reviewers will assess the risk of bias and the certainty of the evidence. Discrepancies will be resolved by consensus.

Strategy of data synthesis: The characteristics of the studies will be described in tables. Estimation of the intervention effect will be done through a random effects model and expressed as mean differences, or standardized mean differences when different scales were used, for continuous data. In the case of dichotomous data, the effect estimate will be expressed as relative risk. The degree of heterogeneity will be estimated through the I2 statistic. A value between 25% and 50%, 50% and 75%, and greater than 75% of I2 correspond to low, moderate and high levels of heterogeneity respectively. We will be used the Review Manager® software. Publication bias was assessed by visualizing a funnel plot, and Begg's and Egger's tests for the possible existence of small study bias using RStudio® software.

Subgroup analysis: If possible, we will perform the following subgroup analyses: 1) By type of ventilatory support: NIV or invasive MV; 2) By electrostimulation dosage: as reported by the included studies.

Sensitivity analysis: If possible, we will perform sensitivity analyses excluding (1) studies with a non-RCT design and (2) studies where it was necessary to calculate outcome data from the information provided by the corresponding studies (e.g. calculation of the mean from the median).

Language: Our search will not be limited by the language in which the studies are published.

Country(ies) involved: Chile.

Keywords: COPD; critical illness; ventilatory support; mechanical ventilation; neuromuscular electrical stimulation; functional electrical stimulation.

Dissemination plans: The protocol of this review and its results will be presented at conferences and published in journals related to critical care, rehabilitation and physical therapy.

Contributions of each author:

Author 1 - Ruvistay Gutiérrez-Arias - Lead author. Developed the general idea and wrote the protocol and manuscript.
Email: ruvistay.gutierrez@gmail.com
Author 2 - Yorschua Jalil - Co-author. Reviewed the protocol and manuscript.
Email: yjalilcontreras@gmail.com
Author 3 - Rocío Fuentes-Aspe - Co-author. Reviewed the protocol and manuscript.
Email: rocio.fuentes.aspe@gmail.com
Author 4 - Pamela Serón - Co-author. Reviewed the protocol and manuscript.
Email: pamela.seron@ufrontera.cl